Preterm Oxygenation of the Cerebrum: Key for Erythrocyte-transfusion Threshold, a randomized controlled trial

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON45656

Source
ToetsingOnline

Brief title
POCKET-study

Condition

- Other condition
- Anaemias nonhaemolytic and marrow depression

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: neurological outcome, preterm infants, red blood cell transfusion, threshold

Outcome measures

Primary outcome

The primary outcome measure will be the neurological outcome at the age of three months post term, based on the motor optimality score (MOS) of the quality of General Movements (GMs).

Secondary outcome

Secondary outcomes will be the prevalence of in-hospital mortality and morbidities NEC, BPD, ROP, and deterioration of IVH assessed at 3 months post term age. Urinary I-FABP levels will be measured to determine intestinal cell damage as early marker for NEC. Cerebral regional tissue oxygen saturation and the total amount of RBC transfusions during the study period of 4 weeks will be recorded.

Study description

Background summary

Neonatal anemia is common in preterm infants. During their stay in the neonatal intensive care unit, most of these high-risk infants receive at least one red blood cell (RBC) transfusion. The RBC transfusion for the anemic infant is an intervention that rapidly improves oxygen transport to vital organs, such as the brain, the gut, and the kidneys. There are also complications of the RBC transfusion. Besides risks of transfusion reactions, RBC transfusions are associated with an increased risk of necrotizing enterocolitis (NEC),

bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), deterioration of intraventricular hemorrhage (IVH). These complications lead to an increased mortality and impaired neurodevelopmental outcomes. The lack of knowledge on the balance of potential benefits and risk of RBC transfusion for anemic infants, have led to controversies about the optimal threshold for RBC transfusion for this population.
The current guidelines for RBC transfusion are based on thresholds of hemoglobin (Hb) values. According to protocol, clinical variables are not taken into account regarding the indication, with the exception of requirement of artificial ventilation. Sufficient oxygen saturation in vital organs, however, may justify withholding the transfusion despite lower Hb levels. Recently, measuring tissue oxygen saturation has proven valuable in preterm and term infants, and has become part of routine clincial care. Tissue oxygenation can be continuously and non-invasively measured by near-infrared spectroscopy (NIRS).
We intend to conduct a randomized controlled trial, comparing two treatment strategies for RBC transfusion in preterm infants. We will compare a newly developed strategy for treatment of preterm anemia with the current treatment strategy. In the new strategy, transfusion Hb thresholds will be lower by 1 mmol/l, provided adequate cerebral oxygen saturation values are met.

Study objective

Our primary objective is to test our hypothesis that lower Hb thresholds than the current ones, provided adequate cerebral oxygen saturation values are met, will lead to a better neurological outcome in preterm infants at three monts post-term.
Our second objectives are to test the hypotheses that lower Hb values for RBC transfusion will lead to less in-hospital mortality and a smaller prevalence of NEC, BPD, ROP, and deterioration of IVH. Furthermore, we will evaluate whether cerebral oxygen saturation values remain within safe limits in the intervention group. Finally, we will test our assumption that the intervention strategy indeed leads to less RBC transfusions during the study period.

Study design

This study will be a randomized controlled trial (RCT).

Intervention

The intervention group will not receive a RBC transfusion (15-20 ml/kg leukocyte-reduced erythrocytes) in case of an Hb threshold which is 1.0 mmol/l lower than current guidelines, i.e. at an Hb threshold of 7.0 mmol/L or 6.0 mmol/L depending on ventilatory support, unless cerebral regional tissue oxygen saturation is lower than 72% for at least 30 consecutive minutes during the first four weeks after birth, or until discharge. The control group will be

treated according to current clinical NICU guidelines with the threshold for RBC transfusion: Hb < 8.0 mmol/L if the infant is ventilated, and Hb < 7.0 mmol/L if not.

Study burden and risks

This study cannot be performed in another population, as the controversies about the threshold for RBC transfusion are typical for anemic preterm infants.
Burden: All infants participating in the study are subjected to routine neonatal intensive care. The study intervention poses minimal extra burden on the patients for several reasons. First, monitoring of cerebral regional tissue oxygen saturation is routine clinical care in all preterm infants admitted to the NICU at the UMCG, and NIRS is a continuous and non-invasive method to use. For the purpose if this study, extra NIRS measurements will be needed in the time periods that Hb is near intervention and standard thresholds, when cerebral oxygen saturation dictates the need for RBC transfusion.
Second, evaluating GMs is a widely accepted non-invasive method to assess the neurological neonatal outcome. At 3 months post term the infant will be video-recorded during an outpatient clinical visit or at home for 10 minutes, with the infant in a actively awake state, comfortably dressed, with uncovered arms and legs.
Third, the urinary samples will be collected by a small gauze in the diaper. This is also a non-invasive method. The samples will be collected during routine handling moments, so the infant will not be disturbed.
Benefits and risks: The supposed new treatment strategy may reduce the total number of received RBC transfusions, and may subsequently reduce the prevalence of RBC related morbidity. Conversely, a lower Hb threshold for RBC transfusion might increase the severity and duration of anemia, which is also associated with poorer outcomes. The studies investigating these lower Hb thresholds had even lower thresholds than in our intervention group. Moreover they did not take cerebral oxygen saturation values into account. Both evidence for serious side effects of RBC transfusion and of severe anemia has led to equipoise and justifies in our opinion performing our proposed RCT.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

- gestational age < 32 weeks
- age between 0-7 days
- written informed consent by legal representative(s)

Exclusion criteria

- chromosomal abnormality (e.g. trisomy 13,18,21)
- perinatal asphyxia resulting in Apgar score < 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)
- diagnosis of NEC prior to inclusion
- intraventricular and periventricular hemorrhage > grade 2 according to Papile, 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 phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-07-2018
Enrollment:	194
Type:	Actual

Ethics review

Approved WMO Date:	28-03-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-09-2019
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: 22948
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL60383.042.17
Other	NTR registratie is in gang gezet
OMON	NL-OMON22948