After necrotizing enterocolitis in preterm infants: The time to reach full enteral feeding and its relation to intestinal recovery and neurocognitive development.

Published: 23-12-2014
Last updated: 21-04-2024

The aim of the study is to gain more insight in the course of intestinal oxygenation, urinary I-FABP concentration, and plasma Citrulline levels (as markers for intestinal damage and recovery) after NEC in relation to time to full enteral feeding...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Observational non invasive

Summary

ID

NL-OMON40857

Source
ToetsingOnline

Brief title
Post-NEC study

Condition

- Gastrointestinal inflammatory conditions
- Neonatal and perinatal conditions

Synonym
Intestinal inflammation of the preterm infant, NEC

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: Near-infrared spectroscopy, Necrotizing enterocolitis, Neurodevelopmental outcome, Time to reach full enteral feeding

Outcome measures

Primary outcome

Our main study parameters are based on the following questions:

- Intestinal oxygen saturation (and extraction) measured with NIRS and the time

it takes to reach full enteral feeding after developing NEC

- The measurement of urinary I-FABPs and the time it takes to reach full

enteral feeding after developing NEC

- The measurement of plasma citrulline and the time it takes to reach full

enteral feeding after developing NEC

Our main study parameters consist of:

- Intestinal oxygen saturation (rintSO2)

- Intestinal FTOE

- Concentration of urinary I-FABP

- Plasma Citrulline levels

Secondary outcome

Our second objective is to assess the relation between the time it takes to

reach full enteral feeding (more or less than 10 days) after developing NEC and

neurodevelopmental outcome measured with the assessment of the quality of GMs

(and the calculation of the motor-optimality score) at the term and three

months post term age.

The study parameter to answer our second objective is:

- Quality of general movements (motor-optimality score)

Study description

Background summary

Necrotising enterocolitis (NEC) is a common but devastating disease mainly occurring in preterm infants. Neurodevelopmental outcome is significantly poorer in NEC survivors when compared to their peers without NEC. Reduced (cerebral) growth due to feeding problems after NEC might add to this impaired development. Several studies reported on the importance of enhanced nutrition in very preterm infants to stimulate brain growth and neurodevelopmental outcomes.
A major concern for neonatologists and surgeons is the timing of reintroducing enteral feeding after the infant had developed NEC, during which nil per os (NPO) is prescribed. It is not clear how to approach the delicate balance between undernutrition, delayed growth and impaired neurodevelopmental outcomes later on one hand, and the risk of re-introducing enteral feeds after NEC too early, with the intestines still damaged and unable to digest feeding on the other. Refeeding too early might lead to an aggravation of the inflammation of the bowel wall or recurrent episodes of NEC and possibly gut-related septicaemia. Due to the lack of any evidence regarding optimal time and pace of reintroducing enteral feeding after NEC, current refeeding protocols are only consensus based.
Several methods might help to assess the quality of the intestines during and after NEC, of which Near-InfraRed Spectroscopy (NIRS), the measurement of urinary intestinal fatty acid binding proteins (I-FABPs), and plasma Citrulline levels, are three validated methods for assessing bowel wall damage. NIRS measures the regional intestinal oxygen saturation as surrogate for perfusion. Because NEC is associated with low intestinal perfusion and ischemia, NIRS may provide information for intestinal recovery. I-FABP is a protein present in the epithelial cells of the small and large intestines, and is released immediately after intestinal epithelial cell damage and excreted by the kidney. This makes I-FABP a potential reliable marker for the detection and progression of NEC. Citrulline is a free amino acid synthesized in the liver and small intestine and found in human plasma. Lower plasma Citrulline levels are associated with a

reduced function of enterocytes and lower absorptive capacity of the small intestine. Recent studies showed low plasma Citrulline levels in preterm infants with NEC. This makes Citrulline another potential marker for the evaluation of the recovery of the intestine.
A method to evaluate the neurodevelopmental state of those infants who developed NEC, is the assessment of the quality of general movements of the infant (to predict long-term outcome). With the assessment of the general movements a motor-optimality score (MOS) can be calculated and compared with the norm.
The aim of this study is to gain more insight in the intestinal recovery after NEC, measured by NIRS, plasma Citrulline levels, and urinary I-FABPs, in relation to the period to reach full enteral feeding after NEC. Furthermore, we will relate this period to reach full enteral feeding to neurodevelopmental outcome, measured by the assessment of general movements. **

Study objective

The aim of the study is to gain more insight in the course of intestinal oxygenation, urinary
I-FABP concentration, and plasma Citrulline levels (as markers for intestinal damage and recovery) after NEC in relation to time to full enteral feeding and to relate this time to full enteral feeding to neurocognitive outcome.
Our primary objective is to assess the relation between cerebral and intestinal oxygen saturation and extraction measured with NIRS, the measurement of urinary I-FABP concentration, plasma Citrulline levels, and the time it takes to reach full enteral feeding.
Our second objective is to assess the relation between the time it takes to reach full enteral feeding after developing NEC and neurodevelopmental outcome measured with the assessment of the quality of general movements.

Study design

This study will be a prospective observational cohort study. Thirty-two preterm born infants admitted to our neonatal intensive care unit in the UMCG, Groningen, with a gestational age below the 37 weeks who develop NEC with radiological signs of pneumatosis intestinalis will be enrolled.

When radiological signs of pneumatosis intestinalis are confirmed by the radiologist, urine samples from the diaper and intestinal near-infrared spectroscopy measurements (NIRS) during two hours will be performed every day during the NPO period. After reintroducing enteral feeding, urine samples from the diaper and intestinal NIRS measurements during two hours will also be performed once every day. Both, urinary sampling and the measurements with NIRS will continue until the infants reached full enteral feeding or to day 36 after inclusion, whichever comes first.
To measure the plasma Citrulline levels during the period after NEC, we need to

sample 100 microliter blood. This will only be performed when blood will be drawn for clinical purposes. Measurement of plasma citrulline will ideally be done within 48 hours after radiologically confirmed pneumatosis intestinalis as a radiological sign of NEC, once/twice during the nil per os period, at the time when minimal enteral feeding will be reintroduced followed by a measurement once a week, with the last measurement on the day that full enteral feeding is reached or on day 36 after inclusion, whichever comes first. Furthermore, in enterally fed infants, blood samples should be obtained one hour before feeding to avoid postprandial fluctuations of plasma amino acids. Citrulline levels will be assessed with LC-MS analysis.
Finally, a video record will be made to assess the quality of general movements at term age and at the age of three months post term.

Study burden and risks

This pilot study is an observational study, implying minimal extra care; therefore there is almost no burden or risk associated with participation. The study contains four major parameters, i.e. intestinal NIRS measurements during two hours daily, urinary I-FABP samples, plasma citrulline concentration and the motor-optimality score from the assessment of the quality of GMs.
Firstly, NIRS is continuous and non-invasive method and monitoring rcSO2 is already routine clinical care in infants with NEC admitted to the NICU at the UMCG. For the purpose of this study a second sensor will be placed infra-umibilical on the abdomen of the infant using special gauze (Mepitel®) so that skin irritation is avoided. The sensors will be placed and removed only during routine handling moments, so the infant will not be disturbed. Previous studies have demonstrated that this does not hamper routine care and that it is not a burden for the child. We previously showed the benefit of using NIRS to assess cerebral and intestinal oxygen saturation in premature infants with NEC. Starting to measure the rintSO2 within several hours after NEC diagnosis can distinguish infants who might develop severe NEC, needing surgical treatment (registered in the Dutch Trial Registry under NTR3239, METc 2010/038) (10). Additionally, cerebral oxygen saturation is possibly an indicator for the level of illness of the infant. This is why cerebral oxygen saturation measurements are standard clinical care.
This confirms the diagnostic additive value of starting directly with the measurements. Furthermore, it is not known when the intestine starts to recover or when the intestine gets even worse. Without measuring from the start, baseline values are missing, and the point of recovery or worsening can be missed very easily.
Given the minimal burden and risks for the patient and the proven additive value for predicting the severity of the diagnosed NEC, we consider this non-invasive method to be very important in the period after the onset of NEC.
Secondly, collecting samples of urinary I-FABPs will be performed by a little gauze in the diaper. This is non-invasive and will not be a burden to the infant. The samples will be collected during routine clinical care to not disturb the infant. Again, we have wide experience in this method of collecting

urine, which does not affect the infant in any way. I-FABP concentration will be determined using a standard commercial ELISA.
Thirdly, we intend to measure plasma Citrulline levels during the period after NEC by sampling 100 microliter extra blood, only when blood will be drawn for clinical purposes. Measurement of plasma citrulline will ideally be done within 48 hours after radiologically confirmed pneumatosis intestinalis, once or twice during the NPO period, at the time when minimal enteral feeding will be reintroduced followed by a measurement once a week, with the last measurement on the day that full enteral feeding is reached or on day 36 after inclusion, whichever comes first. Citrulline levels will be assessed with Liquid chromatography-mass spectrometry (LC-MS).

Finally, GMs is a widely accepted non-invasive method to assess neurological neonatal outcome. At the age of term and three months post term the infant will be filmed during an outpatient clinical visit or at home. The infant has to be relaxed and comfortable for a successful GMs analysis. The infant has to have little clothes on (romper) so that every movement is visible. Temperature of the environment will be adapted to this situation. The camera will be placed in a way that parents or the infant will not be hindered.

This pilot study may provide more insight into intestinal recovery after developing NEC in preterm infants, which might be of importance to determine the best time to start reintroducing enteral feeding, and to improve growth and eventually neurodevelopmental outcome in those infants.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria: Infants with a gestational age <37 weeks with confirmed pneumatosis intestinalis on x-ray, or suspected NEC > Bells stage 1, admitted on the NICU in Groningen.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
Large chromosomal abnormalities
Intraventricular hemorrhage/Perventricular hemorrhage >grade 2
Use of dexamethason
Congenital heart deformities other than patent ductus arteriosus
Abdominal wall defects/other congenital gastroenteral deformities (ie atresia, microcolon)
Parents/caretakers who are unable to understand Dutch or English

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):	06-01-2015
Enrollment:	32
Type:	Actual

Ethics review

Approved WMO Date:	23-12-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-02-2016
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

No registrations found.

In other registers

Register	ID
CCMO	NL49879.042.14