Cerebral monitoring during neonatal surgery for non-cardiac congenital anomalies: a first step to improve outcome?

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The primary objective of the study is to assess (acute) brain injury in the perioperative phase by cerebral MRI in infants with non-cardiac congenital anomalies requiring surgery in the neonatal period.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital and peripartum neurological conditions
Study type	Observational non invasive

Summary

ID

NL-OMON38736

Source
ToetsingOnline

Brief title
Neonatal brain monitoring during surgery for congenital anomalies

Condition

- Congenital and peripartum neurological conditions
- Gastrointestinal therapeutic procedures

Synonym
birth defects, congenital anomalies

Research involving
Human

Sponsors and support

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

Intervention

Keyword: brain, congenital anomalies, newborn infant, surgery

Outcome measures

Primary outcome

The aim of our study is to assess brain injury using cranial ultrasound (cUS) and cerebral magnetic resonance imaging (MRI). The primary outcome parameter is defined as difusion weighted imaging (DWI) abnormalities in order to evaluate acute brain injury from hypoxic-ischemic events and alterations in cerebral perfusion and oxygenation.

Secondary outcome

Main study parameters/endpoints:

The primary endpoints of this study are:

a. Brain injury diagnosed using cranial ultrasound (cUS) and cerebral magnetic resonance imaging (MRI).

Secondary endpoints consist of:

a. Evaluation of the value of biomarkers for neuronal injury (i.e. S100B, NSE, B-FABP, neuroketal), oxidative stress (NPBI and 8-isoprostane) and inflammation (luminex) in predicting timing of (hypoxic-ischemic) brain injury during neonatal surgery.

b. Neurodevelopmental outcome at 24 months corrected age, measured by Bayley

Scales of Infant and Toddler Development, Third Edition (BSID-III).

Other study parameters are:

Perioperative details about the anesthetic regimen, vital signs, and aEEG and NIRS data will be collected and analysed in relation to brain injury, in order to identify associations between perioperative parameters and potential brain injury. In addition, a detailed medical chart review will be performed and perinatal and demographic data will also be collected and analysed in relation to potential brain injury, in order to find patterns and associations between perinatal, demographic and perioperative parameters and the primary outcome measure.

Study description

Background summary

Infants with non-cardiac congenital anomalies, e.g. esophageal atresia, duodenal atresia, anorectal malformation, abdominal wall defects, choanal atresia, require major surgical interventions in the neonatal period. Concerns have been raised about the potentially deleterious effects of surgery on neonatal brain development. Surgery may be associated with stress, systemic inflammation and respiratory, hemodynamic, and metabolic events that may result in brain injury and subsequent neurodevelopmental impairment. Laboratory work suggests that exposure to general anesthetic agents in critical periods of brain development causes increased neuronal apoptosis and changes in the morphology of dendritic spines in animals. Clinical implications of these findings are, however, unclear. Outcome after neonatal cardiac surgery has been well described; however, little is known about outcome after surgery for non-cardiac congenital anomalies (NCCA).
One of the reasons for the lack of knowledge about brain injury and neurodevelopmental outcome after surgery for NCCA is that infants with congenital anomalies are usually excluded from studies. An association between neonatal surgery and neurodevelopmental impairment has been reported in both term and preterm infants. Furthermore, in recent years cases of severe brain

injury - even after relatively minor surgical procedures, such as inguinal hernia repair - have come to our attention and have raised great concern (nationally collected data, not published yet).

Neuroimaging (cranial ultrasound and cerebral magnetic resonance imaging (MRI)) has been integrated in standard neonatal intensive care practice for years and has been of great importance for improving neonatal care. Neuroimaging has shown to be useful in predicting outcome, clinical decision making and initiating early neurodevelopmental intervention strategies in both term and preterm infants. However, to date neuroimaging has not been implemented in routine clinical care for infants undergoing neonatal surgery. The lack of knowledge of neurodevelopmental outcome and cerebral monitoring in this high-risk group of infants is reason for concern, but can be explained by the lack of awareness in current medical practice and by the lack of coverage by insurance companies. The incidence and severity of brain injury following neonatal surgery is therefore unclear. It is however highly important to gain insight into this matter, because comparable to very preterm infants and asphyxiated neonates, infants undergoing neonatal surgery for congenital anomalies are at risk for neonatal brain injury. Fortunately, we now have the opportunity to extend standard clinical care in this vulnerable group of infants by implementing neuroimaging and neuromonitoring in the routine care process thanks to a grant from a Dutch insurance company.

Standard perioperative care involves monitoring of the infant*s respiratory, metabolic and hemodynamic status by continuously or continually assessing arterial oxygen saturation, arterial blood pressure, heart rate, end tidal CO2, FiO2, respiration rate, blood sample analysis, serum glucose, etc. However, none of these modalities provide the clinician with direct information about perfusion, oxygenation, and functioning of the brain. In our hospital, standard perioperative care is extended with amplitude-integrated electro-encephalography (aEEG) for real time assessment of electrophysiological functioning and cerebral near-infrared spectroscopy (NIRS) to provide continuous and noninvasive monitoring of cerebral oxygen supply and extraction.

Biomarkers for oxidative stress, inflammation, and neuronal injury have been used in clinical research settings to evaluate brain injury in asphyxiated newborn infants. These biomarkers are measured at different time points after a hypoxic-ischemic event to assess timing of neonatal brain injury.

Study objective

The primary objective of the study is to assess (acute) brain injury in the perioperative phase by cerebral MRI in infants with non-cardiac congenital anomalies requiring surgery in the neonatal period.

Study design

This is a single-center observational prospective cohort study in the NICU and PICU of the Wilhelmina Children*s Hospital, University Medical Center Utrecht (UMCU), the Netherlands evaluating (acute) brain injury after surgery for non-cardiac congenital anomalies in newborn infants.

Study burden and risks

There has been increasing concern about the potentially detrimental effects of neonatal surgery on neurodevelopmental outcome, as an increasing number of studies have shown an association between neurodevelopmental impairments and neonatal surgery for NCCA. Moreover, distressing cases of newborn infants with major brain injury even after minor surgery have come to our attention in recent years. In our hospital the decision was therefore made to provide best clinical care by adding neuromonitoring using MRI, cUS and perioperative aEEG and NIRS to standard care for this vulnerable group of infants. In this way, we will be informed about cerebral alterations that may occur in the perioperative phase. In this study, we will evaluate the incidence and extent of potential brain injury as a result from neonatal surgery for non-cardiac congenital anomalies. We will also aim to identify risk factors and potential early markers for brain injury. Moreover, we will aim to evaluate the impact of perioperative brain injury on neurodevelopmental outcome.

The burden and potential risk of this research are considered to be negligible and in proportion to the potential value of the study. This study involves the combination of research procedures and routine clinical procedures. Collecting urine samples and blood samples for measurements of biomarkers of oxidative stress, neuronal injury and inflammation will be a research procedure. Neuromonitoring using cerebral MRI, cUS, aEEG, and NIRS are part of routine clinical care. Neurodevelopmental follow-up are also part of routine clinical care.

There are no risks associated with collecting urine and blood samples. Blood samples will be collected from indwelling arterial catheters and urine samples will be collected from already inserted urinary catheters or from a gauze placed in the infant*s diaper. Both urine and blood samples will only be collected during clinical handling and no extra handling of the infant will be performed.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Infants with non-cardiac congenital anomalies requiring surgery in the first 28 days of life.
Congenital birth defects include for example:
1. esophageal atresia or trachea-esophageal fistula
2. congenital diaphragmatic hernia
3. intestinal atresia
4. anorectal malformation
5. Hirschsprung disease
6. malrotation/volvulus
7. abdominal wall defects (gastroschisis, omphalocele)
8. biliary atresia
9. congenital hydronephrosis
10. Pierre Robin sequence
11. choanal atresia

Exclusion criteria

Custodial parent(s) or guardian with insufficient Dutch language proficiency.

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-01-2014
Enrollment:	210
Type:	Actual

Ethics review

Approved WMO

Date:	15-10-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO

Date:	29-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL43225.041.13