Neonatal Estimation Of Brain Damage Risk And Identification of Neuroprotectants (NEOBRAIN)

Published: 04-03-2008
Last updated: 10-05-2024

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

Summary

ID

NL-OMON31644

Source
ToetsingOnline

Brief title
NEOBRAIN

Condition

- Congenital and peripartum neurological conditions
- Neonatal and perinatal conditions

Synonym
preterm birth

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Bioanalyt, Germany; ,Biocrates,

Austria,BrainZ, New Zealand; ,Europese Unie,Neuropharma Spain,Theraptosis, France;

Intervention

Keyword: brain, damage, preterm, risk factors

Outcome measures

Primary outcome

Primary outcome measures: Brain white matter damage (WMD, defined by MRI, US, EEG)

There is no single parameter that can be seen as an endpoint in this clinical part of the study. All the different biomarkers (EEG/ proteomics and metabolomics) will be investigated for being the best predictive marker for white matter injury that will be seen on the MRI performed at the term equivalent age. Following on to this, it will be studied whether these markers will also be predictive for the neurodevelopmental outcome as tested at two years of age with a BSID-III.

Secondary outcome

Developmental assessment at 2 years of age, using a full neurological examination and the BSID-III

All children will be seen in the follow-up clinic, which is routinely done within the scope of the LNF (Landelijk Nederlandse Follow-up).

Study description

Background summary

The number of surviving extremely low gestational age newborns (ELGAN) is steadily incerasing with limit of viability going down to 23 or even 23 weeks

gestation in some countries. With this increase in survivors and a decrease in mortality, we are faced with an ever increasing number of infants with mild to severe disabilities
Prevention of perinatal brain damage is of major importance for public health and obviously for individual well being. Both white and grey brain matter are affected in perinatal brain damage observed in preterm infants.
Longterm-consequences of extreme prematurity are devastating, and perinatal brain damage clearly plays a role in this scenario. The current pathogenetic paradigm of perinatal brain damage in preterm infants has multiple inter-related aspects and includes
infection/inflammation, hypoxia-ischemia, excitotoxicity, and free radicals. It is likely that these mechanisms do not act alone, but in concert.
The absolute number of neurological handicap of perinatal origin is increasing in Western countries due to increasing survival of preterm infants. The major brain lesions associated with cerebral palsy (CP) and cognitive impairment are white matter damage (WMD) mostly occurring in very preterm infants (born below 32 weeks of gestation) and cortico-subcortical lesions mostly observed in term infants. For financial, technical, and ethical reasons, the pharmaceutical industry has difficulties in making substantial investments in this area, which has left perinatologists with a limited therapeutic
arsenal. At the present time, despite major improvements in neonatal care, there are no established therapeutic regimens that are successful for the prevention or treatment of perinatal brain lesions.
Nevertheless, epidemiological and experimental data have allowed identifying potential targets for neuroprotection. New animal models, such as those employed in NEOBRAIN, will help identify neuroprotective strategies in the newborn.

Study objective

Objective #1: Implement clinical platform. We see the need to implement a clinical platform for two purposes. First, we want to design a biomarker profile of perinatal brain damage in human newborns (see above). Thus, we have established a functional network of institutions caring for newborns that can serve as the basis for such a clinical study designed to identify human biomarker profiles based on genetic and biochemical markers, electroencephalographic
(EEG) patterns, and magnetic resonance imaging (MRI). Second, we will use and expand this platform for clinical drug testing both within the 36 months of NEOBRAIN and thereafter.
Objective #2: Prepare for drug testing
NEOBRAIN is going to pave the way for clinical drug development. In essence, it is our 3rd objective to design our clinical platform in a fashion that allows for quick expansion (i.e., recruitment of further centers), so that bench-to-bedside translational steps (i.e., a clinical trial) can be taken quickly after NEOBRAIN is finished. Indeed, we will prepare for the possibility that this might be the case even within the three years of NEOBRAIN.

Study design

Cohort study
The clinical component of NEOBRAIN will aim at recruiting between months 12 and 24 a first small cohort of 300 newborns with a gestational age <28wks. These infants will come from intensive care units in Hannover, Gothenburg, Paris, Geneva, Berlin, Utrecht, Siena, Innsbruck, Lund and Uppsala (Partners 1, 2, and 7-13).
For biomarker measurement, it will be our foremost goal to obtain the smallest possible sample in order not to burden the baby beyond what is absolutely necessary. The exact procedures were determined in a discussion about these issues at the kick-off general assembly meeting (October 2006), where we devoted considerable time and energy to optimize the amount and timing of blood sampling for the NEOBRAIN clinical study. We are confident that we can measure all the biomarkers we need in a few cc*s (ml*s) of blood.
Since we need early postnatal risk information, we will obtain samples for biomarker measurements at birth (cord blood), and within the first 3 days of postnatal life. To monitor changes, a third sample will be obtained at term for all infants. Since we wish to be cost-effective, the hypothesis-generating component will include genomic (mRNA) analysis only for the first 150 infants. Once we have identified markers of interest, we will use stored samples for further analyses in the hypothesis-testing component using all samples available. Metabolomic and proteomic sampling will be performed in all infants recruited to the study.
Obviously, genetic (single nucleotide polymorphism, SNP) information needs to be obtained only once. We will attempt also to receive permission from parents for parental SNP sampling. In this fashion, we can restrict SNP analyses to markers of interest, identified in the hypothesis-generating component of the study.
Ultrasound scanning and MRI-scans, as well as electroencephalographic (EEG) measurements will be performed according to protocols to be developed over the first months of NEOBRAIN by respective colleagues from/in the pertinent Work Packages.
At baseline and during the hospitalization of these infants, demographic, socio-economic, clinical, and
morbidity information will be entered from each site using a remote data entry (RDE) system to be developed for NEOBRAIN in a custom-tailored fashion (see below). Imaging- and EEG-related information, and biomarker information from the laboratory partners/SMEs (mainly Partners 2, 4, and 12) will also be entered into a central database to be maintained in Hannover (P1). The goal is to have all information generated within the clinical component of NEOBRAIN available in one centralized database, so that data management and clean-up can be performed centrally.

Study burden and risks

We ensure the Ethics Review Committee and the European Commission that the clinical component of our research will not lead to an increased clinical risk for the preterm babies included in our study population.
Extremely preterm infants are routinely at risk by being exposed to a large number of clinically indicated noxious stimuli during the neonatal period, including blood sampling and care procedures such as suctioning of the endotracheal tube. It is important to note that our scientific studies attempt not to add to this burden by having the current project designed in a fashion that avoids any additional distress as possible by using clinically indicated examinations and time-points for blood sampling.
The studies and examinations described in the NEOBRAIN proposal constitute parts of standard neonatal intensive care for extremely preterm infants in a majority of the included centers. These methods include ultrasonography, long-term EEG and MRI at term.
Ultrasonography
Ultrasound has for a long time been a standard method, since these infants are at increased risk for developing brain damage, and is usually repeated at least twice during the first week of life and then every week to every second week depending on findings and local standards. In NEOBRAIN, we will systematically collect clinical information from clinically indicated studies. The structured way of performing ultrasonography (using protocols to be developed specifically for the NEOBRAIN project) will contribute to improved clinical performance and be beneficial for the infants. The *(c)linical risks
when performing neurosonography (*) include tissue damage from mechanical compression, desiccation or surface trauma; increased risks of infection during patient handling; and increased risk of hypothermia in neonates* (Barr LL. Clinical concerns in the ultrasound exposure of the developing central nervous system. Ultrasound Biol Med 2001;27:889-892). We assure the Commission that *by instituting a standardized examination and following appropriate patient handling guidelines, the risk of an adverse outcome associated with neurosonography is minimized. The goal in performing a
standardized examination is to apply the ALARA (as low as reasonably achievable) principle to examinations while increasing reproducibility between studies.* (cit.op.)
Long-term EEG monitoring
This method is increasingly used in neonatal intensive care units for clinical intensive-care monitoring of both term and preterm infants at high risk for compromised brain function. The reduced number of electrodes in the EEG-monitor (usually 1 or 2 channels of EEG requiring 3 or 5 electrodes, respectively) gives information on overall brain function as shown by the electrocortical background activity and epileptic seizure activity (which is often entirely subclinical). The EEG will be recorded
through standard disc electrodes or hydrogel (stick-on) electrodes, after brief preparation (light scrubbing of the skin) with Nuprep cream or similar, both are standard procedures (hydrogel electrodes were recently described: West et al. Early Hum Dev 2006;82:43-51). These methods for application of EEG electrodes have been used in a large number of infants without any reported

side effects. They are usually easy and quick to apply and do not seem to disturb the infants.
Magnetic resonance imaging
Neonatal magnetic resonance imaging (MRI) is performed for clinical purposes in many, if not all, participating NEOBRAIN centers for several years. Therefore, we have accumulated considerable collective expertise in MRI techniques, and its associated practical issues. We confirm that MRI performed within NEOBRAIN using a specified protocol to be developed and agreed upon the consortium (see deliverable D6.1 in our proposal). Moreover, we confirm that this protocol will be
designed in a fashion that ensures minimal clinical risk. It goes without saying that we will obtain parental consent.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

preterm infants born with a gestational age below 28 completed weeks.

Exclusion criteria

preterm infants born after 28 completed weeks or born at a referring hospital rather than in the UMC Utrecht
congenital anomalies
chormosomal disorders

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):	27-05-2008
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO

Date:	04-03-2008
Application type:	First submission
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	NL19402.041.07