Dolphin CONTINUE: A nutritional intervention aimed at improving neurodevelopmental outcome in infants at risk for or with early life brain injury

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Congenital and peripartum neurological conditions
Study type	Interventional

Summary

ID

NL-OMON56181

Source
ToetsingOnline

Brief title
The Dolphin Study

Condition

- Congenital and peripartum neurological conditions
- Neonatal and perinatal conditions

Synonym
prematurity

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Health Holland;Faculteit Sociale Wetenschappen Universiteit Utrecht;afdeling neonatologie UMC Utrecht,Nutricia

Intervention

Keyword: Extremely preterm birth, MRI, Nutrition

Outcome measures

Primary outcome

The primary endpoint is white matter microstructure integrity, specifically:

diffusion tensor imaging derived Fractional Anisotropy of white matter tracts

at three months corrected age, analysed using Tract-Based Spatial Statistics

(TBSS).

Secondary outcome

PARCA-R questionnaire at 24 months Communicative Development Inventories at 12

& 24 months Ages and Stages Questionnaire at 12 & 24 months Bayley Scales of

Infant and Toddler Development at 24 months Changes in brain anatomy (volumes,

cortical thickness, etc) on MRI Anthropometry at 0, 1, 3, 12 & 24 months Safety

throughout study

Study description

Background summary

Despite advances in perinatal care, preterm born infants born < 30 weeks of gestation still are at risk for brain injury and subsequent neurodevelopmental delay. The likelihood of brain injury occurring depend on gestational and age as well as on other morbidities. Depending on the cause, location and extent of injury, adverse outcome includes epilepsy, visual impairments, cerebral palsy, intellectual disabilities, learning and attention difficulties and

neuropsychiatric conditions. This injury occurs during a period when their vulnerable developing brain undergoes a massive transformation and can therefore have severe consequences. At the same time this might be a window of opportunity for interventions to harness the brain*s intrinsic plasticity to overcome the consequences of brain injury. It has become clear that prematurity itself can have can have wide spread effects on the developing brain, in even in the absence of focal injury, and can likewise affect neurodevelopmental outcome in these infants. Preterm born infants (< 30 weeks) often show problems at school age, including lower intelligence, attention problems and memory deficits. There are currently no early therapies available for this group of infants. During the last decade, nutrition has received increasing attention as a potential intervention to promote brain development and subsequent outcome. During critical periods of development in fetal and early postnatal life, the brain demands high amounts of nutrients for cell proliferation, differentiation and metabolism, specifically glucose, amino acids, iron and zinc. Several studies have demonstrated that high protein and energy intake improves growth fo the preterm born infant and subsequent outcome. However, there is limited clinical evidence for the effect of nutritional intervention on long term cognitive outcome. This might also be due to the use of single nutrients or the use of nutrients during a brief period of time. The Dolphin concept, a combination of several nutrients such as docosahexaenoic acid, arachidonic acid, choline, vitamines and trace elements has demonstrated to increase the number of synaptic proteins and phospholipids in the brain resulting in increased dendritic spine densities and subsequent improved cognitive outcome in rodents. In two recent clinical trials in infants and toddlers, subjects who received the Dolphin concept also showed a trend towards a better cognitive outcome, though this did not reach significance.

Study objective

The main objective is to study the effect of the nutritional intervention versus the control product on white matter development (as assessed using tract based spatial statistics of fractional anisotropy) using a DTI scan at the corrected age of three months.

Secondary objectives are
- to study the effect of the nutritional intervention versus the control product on cognitive, speech and language, and motor development.
- to study the effect of the nutritional intervention versus the control product on brain anatomy, defined as (sub)cortical volumes, cortical folding, white matter integrity and MR spectroscopy
- to study safety of the study product

Study design

This is an exploratory randomized, placebo-controlled, double blind, parallel

group, multi-center, single country trial. Infants will be randomised between the Dolphin Concept and placebo and will be given the nutritional product for 12 months.

Intervention

Infants will be randomised between the Dolphin concept or placebo for a period of 12 months. The supplement can be added to a normal diet. The Dolphin concept consists of a combination of docosahexaenoic acid, arachidonic acid, choline, vitamins and trace elements.

Study burden and risks

The burden for the infant is limited. It can drink and eat at the moments he/she wants, with the nutritional supplement added.
The infant will undergo a MRI at three months of corrected age. This will take place whilst sedated and with maximum hearing production, minimising the burden to the infant. In our experience at the UMC Utrecht, infants undergo the MRI without any burden whilst sedated. After the MRI they slowly awaken at the neonatology department and will remain admitted until they're awake enough and have had a feed. Infants will be monitored during and after the MRI using a pulseoximeter. At this age the occurrence of desaturation due to shallow breathing is rare and if it occurs, it can easily be restored by tactile stimulating of the infant. However, due to the admission of the infant to the medium care unit after the MRI, it will be a long day for parents.

For parents, the burden will be to add the supplement to the milk or diet every day during 12 months. In addition, parents will be asked to fill in a couple of questionnaires during the duration of the study. The other visits at 12 and 24 months are part of the standard clinical care.
Parents will be receive phone calls (7 in total) during the study. These phone calls will be used to supply information on preparing and dosing the product, answer any questions and ask some questions on adherence, safety, current diet and medication.

It might be that some parents, by using the study product, will find it to be confronting to be reminded of the previous admission of their infant to the NICU, including the risk for a delayed outcome. However, in the previous Dolphin study, parents reported that the found it to be comforting that they could give something to their infant that would be potentially be beneficial for its development.

The burden of the additional time investment is described in E4.

We don't expect that the study will involve any risk for the infants or their parents. In the previous Dolphin study the number of adverse events was

comparable between the Dolphin and the placebo group.

Contacts

Public
Universitair Medisch Centrum Utrecht

Lundlaan 6
Utrecht 3584EA
NL
Scientific
Universitair Medisch Centrum Utrecht

Lundlaan 6
Utrecht 3584EA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Babies and toddlers (28 days-23 months)
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

1. Written informed consent of custodial caregivers 2. Preterm born infant with a gestational age at birth < 30 weeks 3. At least one custodial caregiver masters the Dutch language

Exclusion criteria

1. Any relevant proven or suspected chromosomal anomaly, metabolic disorder or

genetic syndrome
2. Presence of a congenital central nervous system infection or malformation
3.Presence of any congenital gastrointestinal malformation
4. No realistic prospect of survival at the discretion of the attending physician
5. Expected or foreseen inability of the subject*s custodial caregivers to adhere to protocol instructions
6. (Previous) participation in other nutritional intervention studies involving investigational or marketed nutritional products concomitantly or within three weeks prior to start study product intake, that could impact on the main outcome parameters and/or subject safety (at the discretion of the coordinating investigator)
7. Infants who have or are suspected of having a cow*s milk allergy and/or have already started with extensively hydrolyzed milk
8. Infants who have or are suspected of having egg allergy (or products thereof), fish oil allergy (or products thereof) and/or lactose intolerance as these are present in the study product

Given the (potential) long time between enrolment and start of the nutritional intervention the custodial caregivers will be contacted at 2-3 weeks prior to term-equivalent age. At this time, infants can drop out of the study due to the following exclusion criteria:
9. Infants who are not fully enterally fed and/or unlikely to start the nutritional intervention at home or at the peripheral hospital at 40-43 weeks post-menstrual age
10. Infants who are expected to be unable to undergo MRI under sedation at three months of corrected age.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-05-2022
Enrollment:	130
Type:	Actual

Ethics review

Approved WMO Date:	28-10-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	06-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-06-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-11-2023
Application type:	Amendment
Review commission:	METC NedMec

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: 23524
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL72700.041.21
OMON	NL-OMON23524