A randomised, double-blind, controlled trial to evaluate the effects of a nutritional product on brain integrity in preterm infants

Published: 17-08-2016
Last updated: 16-11-2024

>Primary objective:During the intervention period (from randomisation until and including Term Equivalent Age [TEA]): To investigate the effect of the test product vs. the control product given to preterm infants born at 24+0 to Secondary…

Ethical review	Approved WMO
Status	Completed
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON55507

Source
ToetsingOnline

Brief title
NutriBrain

Condition

- Immune disorders NEC
- Bacterial infectious disorders
- Congenital and peripartum neurological conditions

Synonym
brain development in preterm infants, brain maturation in preterm infants

Research involving
Human

Sponsors and support

Primary sponsor: Nutricia
Source(s) of monetary or material Support: Subsidie Universiteit Utrecht en Provincie Utrecht

Intervention

Keyword: brain development, nutrition, preterm infants

Outcome measures

Primary outcome

During the intervention period (from randomisation until and including TEA):

Tract-Based Spatial Statistics analysis using the diffusion weighted imaging to investigate the difference in fractional anisotropy at TEA between the test group and control group

Secondary outcome

During the intervention period (from randomisation until and including TEA):

- White matter injury score assessed according to Kidokoro et al. on T2 and T1 weighted MR images measured at TEA

- Brain tissue volumes (cerebellar, cortical grey matter, unmyelinated white matter, deep nuclear grey matter and ventricular volumes, and extracerebral cerebrospinal fluid) and cortical morphology (sulcation index, cortical surface area, and cortical thickness) assessed on T2 and T1 weighted MR images measured at TEA

- Occurrence of serious neonatal infections (defined as culture proven infection with clinical symptoms of an infection; clinically significant necrotising enterocolitis (defined as Bell*s stage two or higher); and/or meningitis with or without positive culture; or clinical respiratory infection

>= 4 white blood cells per field associated with a specific pathogen in the tracheal aspirates; according to the categories proposed by Stoll et al.) until TEA

- Serum concentrations of specific circulating inflammatory markers such as IL-6, IL-10, TNF-α and IL-8/CXCL8, measured at fixed time points until TEA, optional, and on the condition that blood is sampled at that time-point for routine clinical purposes.

During the follow-up period (after TEA until 24 months corrected age):

- Bayley Scales of Infant and Toddler Development-Third Edition scores on three subscales (cognitive, fine and gross motor) at 24 months corrected age

Study description

Background summary

Despite advances in perinatal care, extremely preterm infants still face significant neurodevelopmental challenges, with over 50% of extremely preterm infants exhibiting cognitive disabilities, behavioural problems and mild to moderate motor impairments. These neurodevelopmental deficits place a major burden on health care and society. Hence, there is an urgent need for neuroprotective strategies to improve outcomes for these children.

During the third trimester of pregnancy, important processes of brain growth and maturation take place with a rapid increase in both white and grey matter volumes and subsequent cortical folding. Moreover, this phase is characterised by rapid development of glial cells and neurons in the white matter. Extremely preterm infants are thus exposed to extra uterine life in a period of critical brain development, especially of white matter structures that render them particularly susceptible to injury. Not surprisingly, white matter injury is the most common pattern of brain injury in extremely preterm infants.

Perinatal infection has been recognised as an important risk factor for white matter injury in preterm infants. In a recent study, Chau and colleagues showed

widespread abnormalities of microstructural and metabolic brain development, in addition to white matter injury in preterm infants with postnatal infections. Compared to preterm infants without infections, infected newborns demonstrated lower FA values predominantly in the posterior white matter, increased average diffusivity, indicating delayed myelination and maturation of the oligodendrocyte lineage, and lower N-acteylaspartate/choline ratios - reflecting impaired neuronal integrity and metabolism. The main pathogenetic mechanism of white matter injury is considered to be inflammation, that may be potentiated by co-existing ischemia.

The impact of nutrition on brain growth and cognition in preterm infants has been increasingly appreciated. Furthermore, in recent years there has been an increasing body of evidence that supplementation of probiotics may be beneficial to preterm infants. Probiotics are micro-organisms that colonise the gut and provide health benefits to the host through improved mucosal barrier integrity, regulation of appropriate bacterial colonisation, and immunomodulation. A recent Cochrane review including 2842 has demonstrated that supplementation of enteral probiotics reduced the incidence of significant NEC (Bell stage >= 2) and mortality, with a relative risk (RR) of 0.35 (95% confidence interval (CI): 0.24; 0.52) for NEC and RR 0.40 (95% CI: 0.26; 0.60) for all-cause mortality. In many level III neonatal intensive care units (NICUs) across the globe, such as in Finland, Japan, Columbia, Denmark, Italy, Germany, New-Zealand, and Australia, supplementation of probiotics has already been integrated into routine clinical practice because of the presumed beneficial effects outlined above.

The combination of probiotics and prebiotics is known to be synergistic, with prebiotics enhancing the survival of endogenous probiotic organisms in the host. The most widely studied prebiotics are galacto-oligosaccharide (GOS), fructo-oligosaccharide (FOS), and inulin. Oligosaccharides represent an important component of human milk and have been assigned important prebiotic, antimicrobial, immunomodulatory and anti-inflammatory functions. Oligosaccharides have the potential to improve the infant*s intestinal microbiota by promoting growth of Bifidobacteria and Lactobacillus, that in turn reduce the burden of potentially pathogenic micro-organisms in the gut.The bifidogenic effect on the gut microbiota may support the immature immune system by establishing an immunologic balance. The immune-modulating capacity of prebiotic oligosaccharides is also likely to be microbiota-independent through direct interaction with immune cells. Because of their presumed health benefits, prebiotic oligosaccharides are supplemented to preterm formula as part of routine clinical care. Meta-analyses of trial data have demonstrated the safety of prebiotic supplementation, yet no convincing evidence was found for a beneficial effect on serious neonatal infections. Therefore, evidence-based recommendations of prebiotics as an isolated supplement, have so far not been made.

Glutamine is the most abundant amino acid in the body. It is considered to be

an important fuel to rapidly dividing cells such as enterocytes and lymphocytes and plays a substantial role in maintaining functional integrity of the gut. Concomitantly, glutamine depletion leads to impaired functional integrity and immune suppression. VLBW infants are at particular risk of glutamine depletion, because they are primarily dependent on parenteral nutrition that contains little to no glutamine. It is therefore postulated that glutamine-enriched nutrition may improve immune function and intestinal integrity in these vulnerable infants. Meta-analysis of trial data from five randomised controlled trials showed a significantly lower incidence of invasive infections in preterm infants who had received glutamine-supplemented enteral nutrition compared to controls. No differences in the incidence of NEC or all-cause mortality were found. Interestingly, a Dutch study (GEEF study) demonstrated long-term benefits on brain development of early enteral glutamine supplementation. VLBW infants who had received glutamine-enriched enteral nutrition in the neonatal period showed larger brain volumes and improved white matter integrity at eight years of age compared to controls. Differences in white matter volume and white matter integrity of the hippocampus measured by FA were strongly associated with the number of serious neonatal infections. Hence, these findings emphasise the impact of neonatal infections on white matter integrity and support the hypothesis that glutamine may improve brain development. To the best of our knowledge, no studies have so far been conducted to assess the impact of probiotics, or prebiotics on neonatal infections and/or inflammation in relation to brain development. This is of particular interest because of the postulated importance of inflammation and infection in the pathogenesis of white matter injury and the well-known association between white matter injury and subsequent neurodevelopmental impairment.

In conclusion, there is substantial evidence for the favourable effect of probiotics on NEC and all-cause mortality in preterm infants. Enteral glutamine supplementation has been shown to reduce the incidence of serious neonatal infections. The benefits of oligosaccharides have not yet been established, as literature shows only circumstantial evidence for a reduction of serious infections in infants that received oligosaccharides as mono-therapy. All three supplements have shown to be safe and no serious side effects have been reported in large clinical trials. To date, there is no literature on the combined effects of these nutritional supplements, or on their impact on neonatal brain development. It is hypothesised that a combination of probiotics, prebiotics, and glutamine may act synergistically. This hypothesis is supported by animal studies in allergic mice, in which the combination of L-glutamine, Bifidobacterium breve (B. breve), and scGOS/lcFOS was demonstrated to exert a more beneficial effect on behaviour than the combination of B. breve and scGOS/lcFOS alone. Therefore, we have decided to combine these ingredients. Oligosaccharides promote survival of probiotics in the host, and may improve the effect of probiotics on immunomodulation and intestinal integrity, in addition to their intrinsic benefits on immune function, host microbiota and mucosal barrier integrity. Glutamine may further enhance these favourable effects. Subsequently, the combination of probiotics,

prebiotics and

Study objective

>Primary objective:
During the intervention period (from randomisation until and including Term Equivalent Age [TEA]):
To investigate the effect of the test product vs. the control product given to preterm infants born at 24+0 to <30+0 weeks gestational age, on white matter microstructure integrity (specifically: Fractional Anisotropy of the white matter tracts, analysed using Tract-Based Spatial Statistics [TBSS]), as assessed using magnetic resonance diffusion tensor imaging at TEA.

>Secondary objectives:
During the intervention period (from randomisation until and including TEA):
To investigate the effect of the test product vs. the control product, given to preterm infants born at 24+0 to <30+0 weeks gestational age, on:
- White matter injury assessed on T2 and T1 weighted MR images at TEA
- Brain tissue volumes and cortical morphology assessed on T2 and T1 weighted MR images at TEA
- Occurrence of serious neonatal infectious morbidity until TEA
- Development of immune function as measured by specific circulating inflammatory markers until TEA (optional)

During the follow-up period (after TEA until 24 months corrected age):
To investigate the effect of the test product vs. the control product, given to preterm infants born at 24+0 to <30+0 weeks gestational age, on:
- Neurodevelopmental outcome at 24 months corrected age as measured by Bayley Scales of Infant and Toddler Development, Third Edition

>Safety and Tolerance objectives:
During the intervention period (from randomisation until and including TEA):
To investigate the effect of the test product vs. the control product given to preterm infants born at 24+0 to <30+0 weeks gestational age, on:
- The occurrence of adverse events and serious adverse events
- Adequate growth
- Number of days of parenteral nutrition, time in days to achieve full enteral nutrition (in the UMC Utrecht defined as 120 ml/kg/day for at least 1 day)
- Feeding intolerance
- Serum glutamine and glutamate concentrations (optional, in a subgroup)

During the follow-up period (after TEA until 24 months corrected age):
To investigate the effect of the test product vs. the control product, given to preterm infants born at 24+0 to <30+0 weeks gestational age, on:
- The occurrence of adverse events and serious adverse events

- Growth velocity and anthropometric z-scores until two years corrected age

Study design

Double-blind, randomised, controlled, parallel-group, single-centre study

Intervention

The intervention comprises a nutritional product that consists of two components (part A and part B).
Test product group will receive:
- Part A: one daily dose of Bifidobacterium breve M-16V (3 x 109 cfu per day for infants with birth weight >=1000 g; 1.5 x 109 cfu per day for preterm infants with birth weight < 1000g until they reach enteral feeds of 50-60 ml/kg/day, then 3 x 109 cfu per day)
- Part B: L-glutamine (0.3g/kg/day) and short chain galacto-oligosaccharides (scGOS)/long chain fructo-oligosaccharides (lcFOS) (9:1) (0.6g/kg/day) supplemented to the regular enteral feed

Control product group will receive:
- Part A: One daily dose of carrier material
- Part B: Carrier material and casein and whey protein hydrolysates supplemented to the regular enteral feed

Study burden and risks

Supplement
Based on previous research, it is believed that use of the test product may lead to a reduction in the infectious and inflammatory burden experienced by premature infants, with subsequent indirect and potentially direct benefits in brain integrity/brain development.

The probiotic and overall prebiotic dosages lie within the range of the tested dosages shown to be safe and well tolerated in premature infants. The L-glutamine dosage has been extensively tested without reported adverse effects in randomised controlled trials in premature neonates.

The only recognised possible adverse reaction associated with probiotic administration is positive culture of the probiotic organism B. breve strain M-16V from a normally sterile site. This is a very rare and unexpected event: with B. breve M-16V it has never been previously reported, and with other B. breve strains it has only been reported once (in an infant with an omphalocele - a condition which is applied as an exclusion criterion in the current study).
The only recognised possible adverse reaction associated with prebiotic administration is mild gastrointestinal discomfort (loose stools, constipation, abdominal pain and/or flatulence). Gastrointestinal discomfort and feeding

tolerance will be closely monitored throughout the intervention period. (For details regarding the above refer to the PIB).

MRI measurements
Potential risks of MRI scanning include noise-related hearing damage, respiratory compromise and feeding problems in the first few hours after scanning. The latter two could only be potentially present if sedation is administered. To minimise the risk of noise-related hearing damage, appropriate hearing protection is applied to the subject*s ears prior to scanning. Sedation involves the potential risk of desaturation, apnea and feeding problems in the first few hours after scanning, due to drowsiness. Although these side effects are rarely reported, appropriate safety measures will be taken, according to the local NICU protocol in case sedation is administered. Under the conditions stated above, MRI scanning is considered a safe procedure. The benefit of scanning at TEA is considered to outweigh the burden, because of the importance for evaluation of the study objective and because even extremely preterm infants tolerate MRI scanning well, if appropriate measures for hearing protection and monitoring - if sedation is given - are taken.

Other study procedures, including sampling
There are no additional risks involved in other study procedures. Blood sampling is considered to be a minimal burden, because it does not involve extra handling of the subject. Samples are collected from indwelling arterial catheters that have been inserted for clinical purposes or - in case the infant does not have an arterial line - during routine sampling for clinical purposes. Some sample material will be reserved for the purposes of the study. In case no blood sampling is done for clinical purposes, blood samples will be omitted. Collecting samples from the skin of the cheek, oral cavity, nasopharynx, and stools is considered a minimal burden. Samples are obtained non-invasively and will preferably be collected in combination with routine clinical sampling in order to minimise handling of the subject and/or burden for the pregnant woman. Moreover, timing of sampling during the intervention period will be dependent on the infant*s clinical condition and stool pattern.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

- Gestational age of 24+0 to <30+0 weeks (by the best estimate of expected date of delivery)
- Less than 72 hours old, and the intention to receive the first administration of study product between 48-72 hours after birth
- Written informed consent from custodial parent(s)

Exclusion criteria

- Any relevant proven or suspected chromosomal anomaly, metabolic disorder, genetic syndrome or congenital central nervous system malformation
- Presence of a congenital central nervous system infection
- Presence of any gastrointestinal malformation
- No realistic prospect of survival
- Concomitant participation in other intervention studies (for example, but not exclusively, those studies involving investigational or marketed nutritional or pharmaceutical products) that could impact on the main outcome parameters and/or subject safety
- Expected or foreseen inability of the subject and/or their families to adhere to protocol instructions
- Admission from an extra regional hospital, unless that hospital is a study site
- Currrent use of gastric inhibitors: H2-receptor antagonists (including ranitidine) or proton pump inhibitors (including omeprazole)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	31-10-2018
Enrollment:	98
Type:	Actual

Ethics review

Approved WMO Date:	17-08-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	18-05-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-08-2018

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-07-2021
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

No registrations found.

In other registers

Register	ID
ISRCTN	ISRCTN96620855
CCMO	NL49902.041.14