The PEPaNIC long-term outcome study: Neurocognitive developmental deficit after critical illness in children: role of modifiable epigenetic changes

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON44273

Source
ToetsingOnline

Brief title
PEPaNIC Follow-up

Condition

- Other condition

Synonym
Critical illness / malnutrition

Health condition

Kinderen die kritiek ziek zijn geweest en behandeld op Intensive Care

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Sophia Research Foundation

Intervention

Keyword: Caloric restriction, Epigenetics, Intensive Care, Long-term neurocognitive outcome

Outcome measures

Primary outcome

The primary goal of the PEPaNIC long-term outcome study is to determine the

long-term neurocognitive outcome (more specifically the IQ-scores, motor and

executive function) of critical illness and the effect hereon of artificial

nutrition provided during the acute phase of critical illness in children.

Secondary outcome

to determine the effect on:

-anthropometrics (legnth, weight, arm-leg circumference)

-neuro-endocrine axes (hair, blood)

-epigenetic modifications (white blood cells / saliva / mucosal swab)

-health economics; eg healthy care consumptions, CUA etc.

-endurance/activity

Study description

Background summary

Rationale: Even after discharge from the hospital these children often continue
to suffer from morbidity for years, with impaired neurocognitive development

and reduced quality of life as the main problems. This *legacy* of critical illness carries an enormous burden for the patient, their family, the healthcare system and society in general. Nutritional support strategies (tolerating caloric deficits versus aggressive nutritional support in the PICU) may play a role in this legacy of critical illness. Controlling blood glucose to fasting normoglycaemia has recently been shown to improve (neurocognitive) outcome in critically ill children 4 years after ICU admission. This tight blood glucose control provoked autophagy and a fasting response in the thyrotropic and somatotropic axes, which related to improved outcome. Caloric restriction in the acute phase of critical illness by delaying the administration of parenteral nutrition reduced morbidity in critically ill adults. We are currently performing a large randomized controlled trial (Paediatric Early versus Late Parenteral Nutrition in Critical illness - PEPaNIC: CCMO projectnr: NL38772.000.12) investigating the short term outcome effects of these different nutritional support strategies. However, metabolism has recently been involved in the regulation of autophagy and epigenetic modifications. Whether caloric restriction, a metabolic intervention, has *carry-over* effects, or metabolic memory by epigenetic changes, leading to a more beneficiary long-term neurocognitive outcome is unknown.

Study objective

We hypothesise that, in comparison with the current practice of aggressive nutritional support, tolerating caloric deficits early during critical illness in critically ill children has *carry-over* effects, through epigenetic changes, that improve long-term (neurocognitive) outcomes.
The primary goal of the PEPaNIC long-term outcome study is to determine the long-term neurocognitive outcome (more specifically the IQ-scores, motor and executive function) of critical illness and the effect hereon of artificial nutrition provided during the acute phase of critical illness in children.
The objectives to be reached within the time frame of this follow-up project are the following:
* Performing a well-designed and sufficiently powered, multi-centre long-term outcome study to investigate the consequences of early versus late parenteral nutrition supplementing insufficient enteral feeding on the neurocognitive outcomes of critically ill children beyond the acute disease course.
* Identifying patient populations that would benefit for long-term outpatient follow-up and care and are currently not offered long-term follow-up in the existing traditional follow-up programs.
* Following, in parallel and longitudinally, matched healthy control children together with the critically ill children to reliably assess the *carry-over* effects of critical illness in comparison with normal ageing over a similar time frame in healthy children.
* Characterising the fasting response on the metabolic profile and the neuro-endocrine axes and mapping the epigenetic modifications in the blood of critically ill children that underlie the differences in long-term outcomes.
With the PEPaNIC follow-up project we aim to add value to the treatment of

critically ill children by the early diagnosis of and counselling in the legacy of critical illness. The novel, nutritional strategy of tolerating caloric deficits could reduce healthcare costs by postponing the administration of expensive parenteral nutrition and by preventing complications in prolonged critically ill patients. As the nutritional strategy may improve neurocognitive development and success in life for critically ill children through epigenetic changes, tremendous costs for society can be saved.

Study design

The primary focus of the PEPaNIC long-term outcome study is neurocognitive development, and more specifically the IQ scores, motor coordination, attention and executive function, at 2 and 4 years after inclusion in the study, in comparison with matched healthy control subjects.

We will compare healthy children with the entire group of children who participated in PEPaNIC as a whole, being a reflection of a paediatric ICU population. The PEPaNIC population is very heterogeneous both in diagnosis, age and in severity of illness, making it representative for a general PICU population. Also, we will analyse the patients according to their randomisation allocation of *early parenteral nutrition* with *late parenteral nutrition* in the PEPaNIC study.

The children will undergo neurocognitive testing (see Table 1 of Protocol), and together with their parents are asked to fill in Health related Quality of Life questionnaires.

Additionally, we will continue to take biological samples (blood, hair, buccal swaps) during these follow-up visits, similar to those that have already been taken during the clinical PEPaNIC trial. These measurements will focus on metabolic markers and the key hormones of the thyrotropic and somatotropic axes. Additionally, the presence of genetic variation, telomere length and epigenetic modifications (histone modification, DNA methylation, micro-RNAs) in white blood cells will be examined and validated for functional relevance with use of mRNA arrays. To investigate the effect on endurance/activity, the participants will perform a walking test and wear an activity measuring device at home during several days.

Study burden and risks

The risk is expected to be futile as it will only entail performing questionnaires and tests and blood draws (separate consent). The burden is expected to be moderate as it will entail a half of day of questionnaires and neuropsychological tests in the outpatient clinic. An additional increase to this burden are the laboratory tests. Separate consent will be asked at different time points for the blood draws at 2 and 4 year follow up. For

patients who are already enrolled in clinical follow-up programs the burden will be less as they are already asked to come to the outpatient clinic and participate in these tests and blood draws. In contrast to the burden there is also a benefit. The long-term follow up will be held as part of already organised follow-up outdoor clinics and which are developed to help children and their parents to recover physically, emotionally and socially after ICU admissions. Aside from the scientific role of our follow-up this clear clinical benefit comes available for all participants, not just those that are traditionally part of an existing follow-up program. For the healthy matched controls there is no clear benefit other than a (neuro)psychological and physical evaluation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Elderly (65 years and older)

Inclusion criteria

The children who are participants in the PEPaNIC study are all eligible for the long-term outcome study.
Healthy controls, recruited for an identical follow-up programme, will be demographically (primarily age, gender and ethnicity) matched to the PEPaNIC study participants.
The inclusion criteria for the healthy controls are:
* Same gender proportion as the cases
* Same age range as the cases
* Same social-economic status

Exclusion criteria

No exclusion criteria, other than 'no consent', are applicable for the PEPaNIC patients. The exclusion criteria for the healthy controls are:
* History of neonatal or paediatric intensive care admission
* History of parenteral nutrition

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-09-2014
Enrollment:	885
Type:	Actual

Ethics review

Approved WMO Date:	04-09-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-06-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-06-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
ClinicalTrials.gov	NCT01536275
CCMO	NL49708.078.14