Darbepoetin for Ischemic Neonatal Stroke to Augment Regeneration

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This study has been transitioned to CTIS with ID 2024-513042-12-01 check the CTIS register for the current data. To perform a double-blind randomized placebo controlled multicenter study with darbepoetin in infants with MRI confirmed PAIS and to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON55870

Source
ToetsingOnline

Brief title
DINOSAUR

Condition

- Central nervous system vascular disorders
- Neonatal and perinatal conditions

Synonym
Perinatal Arterial Ischemic Stroke (PAIS); Neonatal stroke

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: The Research Foundation;Cerebral Palsy Alliance;Australië

Intervention

Keyword: Brain, Darbepoetin, Neonate, Stroke

Outcome measures

Primary outcome

Our primary objective is to determine whether there is a difference in the degree in stroke tissue loss between darbepoetin and placebo treatment, which will be measured by the change in lesion size between the time of onset of the insult and 6-8 weeks of age. Primairy endpoints will be estimated using advanced volumetric magnetic resonance (MRI) techniques, performed within one week after clinical presentation and at 6-8 weeks of age.

Secondary outcome

Secondary objectives:

- We will assess whether there are differences between darbepoetin and placebo treatment in Diffusion Tensor Imaging (DTI) parameters of selected regions of interest. DTI-MRI techniques are performed within one week after clinical presentation and at 6-8 weeks of age.
- We will assess development of USCP, and cognitive development at 18 months of age using the BSID-III scores as well as a full neurological assessment including Gross Motor Function Classification system (GMFCS) and several handfunction tests such as Manual Ability Classification System (MACS), the Hand Assessment of Infants (HAI) and Assisting Hand Assessment (AHA) and compare them between groups (darbepoetin vs placebo).

Study description

Background summary

Perinatal arterial ischemic stroke (PAIS) is an important perinatal cause of long-lasting neurodevelopmental problems. Recent studies report an incidence of PAIS of 1 per 2300 full-term infants born alive. Adverse consequences of PAIS include hemiplegia, cognitive dysfunction, epilepsy and speech problems. In 50-75% of infants, neonatal stroke leads to abnormal neuromotor and -developmental outcome or epilepsy. The estimated annual mortality rate of neonatal stroke is 3.49/100,000 annually. Current treatment options for PAIS mainly focus on controlling convulsions and associated infections. There is no treatment available that leads to reduction of neonatal brain damage in this severely affected group of infants. This leads to life-long consequences of PAIS and forms a large burden for patients and society. The overall aim of this project is to meet this need by developing a treatment strategy. Erythropoiesis-stimulating agents (ESA), such as erythropoietin (EPO) and darbepoetin, have been proven to exert neuroprotection as they can reduce (neonatal) hypoxia-ischemia-induced free radical formation, inappropriate pro-inflammatory and apoptotic activity. EPO also stimulates neuroregeneration via a trophic effect. Several RCTs have been performed in preterm infants with preliminary results showing a positive effect of EPO and darbepoetin on cognitive outcome. Other RCTs are underway in full-term infants with hypoxic-ischemic encephalopathy (HIE). In our centre we performed a pilot study in 20 infants with PAIS, who had open label treatment with EPO showing feasibility and safety. Two other trials with preterm infants and term borns with HIE also showed safety of treatment with darbepoetin in the same dosage as we propose. It has been shown that EPO and Darbepoetin have similar effects, but Darbepoetin is more potent, requires less dosing and is more universally available across countries. The proposed project will undertake an multicenter RCT using Darbe versus a placebo. Successful completion of this project will provide the first evidence of the potential to use ESAs to treat PAIS in newborn infants.

Study objective

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To perform a double-blind randomized placebo controlled multicenter study with darbepoetin in infants with MRI confirmed PAIS and to investigate whether darbepoetin can reduce brain injury in neonates who suffered from perinatal arterial ischemic stroke (PAIS). The ultimate goal of this study is therefore to develop a therapy using ESAs such as darbepoetin to reduce or even prevent lifelong consequences of PAIS-related brain injury in this group of term

newborns.

Study design

Multicenter, double-blind, randomized placebo controlled intervention study in the NICU at the Wilhelmina children*s Hospital / University Medical Centre in Utrecht of (near-)term newborns >=36 weeks of gestation with diagnosis of PAIS (confirmed on MRI within one week of onset of presenting clinical symptoms).

Intervention

One group will be treated with active study medication, darbepoetin (Aranesp), and the other with placebo both consisting of 2 doses of 10microgram/kg/each of intravenous darbepoetin (active treatment) or saline (placebo).

In more detail: After written informed consent, neonates with PAIS will be randomized to two groups: One group will be treated with active study medication, darbepoetin, and the other with placebo both consisting of 2 doses of 10microgram/kg/each of intravenous darbepoetin (active treatment) or saline (placebo). The initial dose will be administered as soon as possible after the MRI diagnosis of PAIS, but within one week after presenting symptoms. The second dose will administered 7 days after the first dose. Blood pressure and heart rate will be monitored during infusion, baseline red and white blood cell samples taken and coagulation status determined.The placebo group will receive 2 dosages of placebo dissolved in an equal amount of fluid as during darbepoetin infusion with a similar infusion time. The infusion scheme is identical as compared to the darbepoetin group (study group). The study and placebo medication either darbepoetin or placebo will be produced and prepared by the local pharmaceutical department. The study medication will be numbered and will not be recognizable by the attending neonatologist (nor the studyteam). In case of signs of suspected adverse reactions of the drug used, the pharmacist of the hospital will have the key to detect whether darbepoetin or a placebo has been administered.

Newborns from other participating centers will be transported to the NICU of the University Medical Center Utrecht after suspicion of PAIS and/or MRI confirmation of PAIS and will undergo the procedures as described above.

Study burden and risks

The extra burden of the present study for the included infants is considered to be very limited to non-existent given the fact that besides the administration of darbepoetin or the placebo, treatment is not different compared to the standard acting treatment protocol for newborns with PAIS. The drug will be administered through an intravenous line which is already in place and one blood sample will be taken at a time when a blood sample will be carried out

for routine clinical care. With respect to possible risks of darbepoetin treatment, the most important potential risk factor such as polycythaemia has been investigated in our own pilot study and did not appear to be present. Other studies with darbepoetin in preterm and term infants did not show any safety risks. Darbepoetin showed similar effects in imporving neurodevelopmental outcome in these infants.
From experimental research and from our own study, we have learned that the complication risk is very low, whereas possibility for a substantial better short- and long-term outcome after PAIS, induced by darbepoetin treatment, seems very realistic on the basis of previous research data.

Contacts

Public
Universitair Medisch Centrum Utrecht

Lundlaan 6
Utrecht 3584 EA
NL
Scientific
Universitair Medisch Centrum Utrecht

Lundlaan 6
Utrecht 3584 EA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Newborns

Inclusion criteria

- Newborns >= 36+0 weeks of gestation, both male and female

- MRI confirmed diagnosis of acute PAIS , in the MCA region with involvement of the cortical spinal tract (e.g. PLIC or peduncles) within one week after the onset of clinical symptoms
- Written informed consent from custodial parent(s)

Exclusion criteria

- Moderate -severe HIE with or without hypothermia therapy ;
- Any proven or suspected major congenital anomaly, chromosomal disorder, metabolic disorder;
- Presence of a serious infection of the central nervous system;
- No realistic prospect of survival, (e.g. severe brain injury), at the discretion of the attending physician;
- Infant for whom withdrawal of supportive care is being considered.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-01-2018
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	darbepoetin
Generic name:	Aranesp
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-11-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-03-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-09-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-03-2023

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-04-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-05-2024
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
EU-CTR	CTIS2024-513042-12-01
EudraCT	EUCTR2015-002997-18-NL
CCMO	NL53975.041.16