Effect of ALlopurinol in addition to hypothermia for hypoxic-ischemic Brain Injury on Neurocognitive Outcome - a blinded randomized placebo controlled parallel group multicenter trial for superiority (Phase III)

Published: 07-03-2017
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This study has been transitioned to CTIS with ID 2024-511322-31-00 check the CTIS register for the current data. To evaluate whether in newborns with asphyxia and early clinical signs of hypoxic ischemic encephalopathy, early postnatal allopurinol...

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

Summary

ID

NL-OMON54639

Source
ToetsingOnline

Brief title
ALBINO-trial

Condition

- Congenital and peripartum neurological conditions
- Neonatal and perinatal conditions

Synonym
brain damage, encephalopathy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Horizon 2020 subsidie

Intervention

Keyword: allopurinol, neonates, neurologic outcome, perinatal asphyxia

Outcome measures

Primary outcome

1. Death

2. Severe neurodevelopmental impairment at the age of two years

Secondary outcome

1. Brain injury assessed by magnetic resonance imaging.

2. Amplitude integrated electroencephalogram and full scale

electroencephalogram.

3. Brain injury at cerebral ultrasound.

4. Laboratory biomarkers and markers of peroxidation.

5. Safety of allopurinol in neonates treated with hypothermia.

6. The pharmacokinetics of allopurinol in neonates treated with hypothermia and

not treated with hypothermia

7. Multi-organ dysfunction before discharge

8. Echocardiography

Study description

Background summary

Perinatal asphyxia is a major cause of death or long-term disability in infants born at term in the western world, affecting about 1-4 per 1.000 life births per year in Europe. Hypothermic treatment became the only established therapy to improve outcome after perinatal hypoxic-ischemic insults. Despite hypothermia and neonatal intensive care, 45-50% of affected children die or suffer from long-term neurodevelopmental impairment. Additional effect is expected with adjuvant earlier neuroprotective interventions, beside hypothermia, this is warranted to further improve their outcome.
Allopurinol is a xanthine oxidase inhibitor and reduces the production of oxygen radicals and brain damage in experimental, animal, and preliminary human studies of ischemia and reperfusion, if administered early after the insult.

Study objective

This study has been transitioned to CTIS with ID 2024-511322-31-00 check the CTIS register for the current data.

To evaluate whether in newborns with asphyxia and early clinical signs of hypoxic ischemic encephalopathy, early postnatal allopurinol compared to placebo administered in addition to standard of care (including therapeutic hypothermia if indicated) improves the neurologic prognosis.

Study design

A placebo-controlled, (double-)blinded, randomized multicenter trial (Phase III)

Intervention

Intervention medication: Allopurinol, powder for injection (PFI), administered in two doses. First dose (20 mg/kg in 2ml/kg sterile water for injection) within 30min postnatal and second dose (10mg/kg in 1ml/kg sterile water for injection) 12 hours thereafter, only if the infant undergoes therapeutic hypothermia.
Placebo medication: Mannitol, PFI, 20mg/kg in the same volume and at the same time intervals as the intervention group - (2nd dose 10mg/kg only if the infant undergoes therapeutic hypothermia).

Study burden and risks

The most important burden to patients are the blood samples. These will be coordinated with clinically required blood samples, preferably collected through an existing arterial or central venous access and the blood loss will be minimal (<2ml/kg in total). The neurodevelopmental follow up at 24 months

may not be standard in the smaller centrums, but this will be only one examination and is most of the times fun for children. In case MRI or EEG is not clinically indicated because of good recovery, we will ask separate informed consent for these examinations. As far as reported in the previous trials of antenatal [Torrance, Pediatrics 2009, Kaandorp, Arch Dis. Childhood F&N 2014] and postnatal [vanBel, Pediatrics 1998, Gunes, Pediatr Neurol 2007, Benders, Arch Dis Child 2006] allopurinol in perinatal asphyxia and high dose allopurinol in other clinical settings in neonates and infants [Clancy, Pediatrics 2001], there is no evidence for significant adverse effects of allopurinol in newborn infants even at high doses. Irritation of the vascular and peri-vascular tissue (transitional redness, swelling and tenderness) may occasionally occur and have uniformly been transient in previous studies However, the pH of allopurinol is high, so a secure intravenous access is essential to prevent extravasation and the consequential possible harm to the patient. The burden and risks are in our opinion acceptable, considering the importance for additional neuroprotection to reduce the mortality and morbidity and the possible benefits for the intervention group.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Newborns

Inclusion criteria

Term and near-term infants with perinatal asphyxia and encephalopathy as defined herein.

Exclusion criteria

- Gestational age below 36 weeks - Birth weight below 2500 g - Postnatal age >30minutes at the end of the screening phase, - Severe congenital malformation or syndrome requiring neonatal surgery or affecting long-term outcome - Patient considered *moribund* / *non-viable* - Decision for *comfort care only* before study drug administration

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:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-05-2018
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	allokid
Generic name:	allopurinol-sodium
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-03-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	26-07-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-02-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-07-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-09-2019
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	04-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-11-2021
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	15-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-05-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-06-2024
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
EU-CTR	CTIS2024-511322-31-00
EudraCT	EUCTR2016-000222-19-NL
ClinicalTrials.gov	NCT03162653
CCMO	NL57237.041.16