CeRebrUm and CardIac protection with Allopurinol in neonates with critical congenital heart disease requiring cardiac surgery with cardiopulmonary bypass

Published: 27-11-2018
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2024-513041-37-00 check the CTIS register for the current data. Primary objective of this study is to significantly reduce relevant (moderate/severe) parenchymatous brain injury on postoperative MRI...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Congenital cardiac disorders
Study type	Interventional

Summary

ID

NL-OMON52736

Source
ToetsingOnline

Brief title
CRUCIAL-TRIAL

Condition

- Congenital cardiac disorders
- Cardiac and vascular disorders congenital
- Congenital and peripartum neurological conditions

Synonym
Brain injury

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMw,Stichting Hartekind;Vrienden van het Wilhelmina Kinderziekenhuis

Intervention

Keyword: Allopurinol, Brain injury, Congenital heart disease, Neonate

Outcome measures

Primary outcome

Primary outcome is a composite endpoint of relevant (moderate/severe) parenchymatous brain injury on postoperative MRI or too instable for postoperative MRI or mortality.

A sample size of 236 patients (both with prenatal and postnatal diagnosis), of which 188 patients with a prenatal diagnosis is needed, when allopurinol is hypothesized to reduce the primary outcome with 20% compared to placebo (two-sided alpha 5%, power 80%). The effect size of 20% is a relevant and viable expectation, and is based on the results of previous neuroprotective studies on neonatal head cooling and allopurinol in neonates with brain injury due to perinatal asphyxia and around cardiac surgery. Primary analysis will be performed with 1 interim analysis at n=118 for the total group and at n=94 for the prenatal diagnosis group, with the option to stop for (1) efficacy, based on O'Brien Flemming type alpha-spending, or (2) futility, based on conditional power analysis. Forty-eight patients with postnatal diagnosis will be enrolled

and secondary analyses for primary outcome assessment.

Secondary outcome

Secondary outcome measures are PK of allopurinol (subgroup); redox and antioxidant state of allopurinol (subgroup); brain injury score and volume of hypoxic-ischemic brain injury (MRI); cardiac function (echocardiography, subgroup MRI); brain function (amplitude integrated electroencephalogram aEEG); brain oxygenation (near-infrared spectroscopy NIRS); motor outcome at 3 months (general movements GMs); cognitive, motor, speech/language outcome at 24 months (Bayley scales of infant development Bayley-III-NL); quality of life at 24 months (TNO-AZL TAPQoL questionnaire); cost-effectiveness of allopurinol at 3 and 24 months.

Study description

Background summary

Neurodevelopmental impairment due to delayed brain development and brain injury is a fundamental problem in children with critical congenital heart disease (CCHD). Significant longterm motor-, cognitive-, and behavioural problems are the result of early postnatally and perioperatively induced brain injury. Allopurinol, a xanthine oxidase inhibitor, prevents the formation of toxic free oxygen radicals, thereby limiting hypoxia-reperfusion damage. Both animal and neonatal studies suggest that administration of allopurinol early postnatally and perioperatively reduces hypoxic-ischemic brain injury, is cardioprotective and safe.

Study objective

This study has been transitioned to CTIS with ID 2024-513041-37-00 check the CTIS register for the current data.

Primary objective of this study is to significantly reduce relevant (moderate/severe) parenchymatous brain injury on postoperative MRI for the total group (both prenatal and postnatal diagnosis) and the prenatal diagnosis

group, which is needed to apply for market registration of allopurinol for this indication in the prenatal diagnosis group. Additionally, to show a beneficial trend in the postnatal diagnosis group. Secondary objectives are to improve cardiac function, brain function and oxygenation and neurodevelopmental outcome and to investigate pharmacokinetics (PK), redox and antioxidant state and cost-effectiveness of allopurinol, and quality of life.

Study design

The proposed study is a phase III, randomized, double-blinded, placebo-controlled, Dutch multicenter trial. All 4 Dutch Pediatric Cardiothoracic Surgery Centers will participate, including (1) University Medical Center (UMC) Utrecht (sponsor), (2) UMC Groningen, and (3) Erasmus Medical Center (EMC) Rotterdam and RadboudUMC Nijmegen.

Intervention

Prenatal diagnosis:
Allopurinol powder for solution for infusion (PFI) 20 mg/kg or mannitol PFI-placebo will be administered early postnatally (within 45 minutes and 12 hours after the first dose), preoperatively (12 hours before surgery), intraoperatively (during start of cardiopulmonary bypass) and postoperatively (24 hours after surgery) to the neonate in case of a prenatal CCHD diagnosis.

Postnatal diagnosis:
Allopurinol PFI 20 mg/kg or mannitol PFI-placebo will be administered preoperatively (12 hours before surgery), intraoperatively (during start of cardiopulmonary bypass) and postoperatively (24 hours after surgery) to the neonate in case of a postnatal CCHD diagnosis.

Study burden and risks

In this study population most of the study procedures are considered as standard clinical care, including echocardiography, aEEG/NIRS (and MRI of the brain, GMs, and BSITD-III-NL within the UMC Utrecht). Study related procedures are MRI of the brain, GMs, BSITD-III-NL (in the participating centers other than UMC Utrecht), and TAPQoL and HTA questionnaires (in all centers). Additionally, only in the UMC Utrecht in a subpopulation blood samples will be taken for determination of pharmacokinetics of allopurinol, and cardiac MRI*s will be performed (immediately after clinically indicated brain MRIs). After completion of the pharmacokinetics sub-study, a redox sub-study with blood- and urine sampling will be carried out in both the UMC Utrecht and the EMC Rotterdam to determine the effect of allopurinol on the redox/antioxidant status.
All prior preclinical and clinical studies in neonates show potential neuro- and cardioprotective effects of allopurinol without relevant side effects. The

potential advantages of allopurinol administration in neonates with critical congenital heart disease outweigh the burden and risks, which are minimal. There is a considerable change that allopurinol reduces (hypoxic-ischemic) brain injury, improves cardiac function and long term neurodevelopmental outcome (quality of life) in the group neonates receiving allopurinol. In addition, the risk on side effects through the study medication is much smaller than the risk on brain injury, lifelong handicaps and death due to the underlying critical congenital heart disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

Neonates with a prenatally or postnatally confirmed diagnosis of CCHD requiring (anticipated) cardiac surgery with CBP within the first 4 weeks of life are

eligible for inclusion. This includes neonates with the following cardiac defects 1) Transposition of the great arteries with or without a ventricular septal defect undergoing arterial switch operation with ventricular septal defect closure if needed; 2) Univentricular hearts: hypoplastic left and right heart syndrome, or variant undergoing Norwood Stage I or Sano palliation; 3) Aortic arch anomalies: interrupted, hypoplastic aortic arch and/or coarctation of the aorta with or without intracardiac defects (ventricular/atrial septal defect, or (sub)aortic stenosis) who undergo complete biventricular repair and/or aortic arch repair; 4) Other variants: truncus arteriosus, total anomalous pulmonary venous connection, or tetralogy of Fallot. Written informed consent of both parents is required prior to inclusion.

Exclusion criteria

- Inability to enroll the patient before the start of delivery in case of prenatal diagnosis, or 24 hours before surgery in case of postnatal diagnosis.
- Doubt whether the aortic arch anomaly before birth requires cardiac surgery with CPB in the neonatal
period.
- Gestational
age below 36 weeks and/or birth weight less than 2000 gram.
- Surgery not requiring cardiopulmonary
bypass.

- Patient considered
moribund.

- Decision for *comfort care only*.

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):	17-02-2020
Enrollment:	236
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Allokid (Acepurin)
Generic name:	Allopurinol 100 mg pfi
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-11-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	25-03-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	18-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-11-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-03-2020
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	04-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-06-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-06-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-06-2024
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	CTIS2024-513041-37-00
EudraCT	EUCTR2017-004596-31-NL
ClinicalTrials.gov	NCT04217421
CCMO	NL62772.041.18