Newborns with congenital diaphragmatic hernia: inhaled nitric oxide versus intravenous sildenafil: an international randomized controlled trial

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IV sildenafil is superior to iNO for the treatment of pulmonary hypertension in CDH newborns and should be considered as the drug of first choice in the future

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neonatal respiratory disorders
Study type	Interventional

Summary

ID

NL-OMON28811

Source
NTR

Brief title
CoDiNOS

Condition

- Neonatal respiratory disorders

Synonym
CDH

Health condition

congenital diaphragmatic hernia pulmonary hypertension newborn congenitale hernia diafragmatica pulmonale hypertensie pasgeborenen

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC
Source(s) of monetary or material Support: Stichting Sophia Kinderziekenhuis Fonds CDH UK the congenital diaphragmatic hernia charity

Intervention

Explanation

Outcome measures

Primary outcome

The absence of pulmonary hypertension on echocardiography on day 14 without pulmonary vasodilator therapy and without treatment failure in patients and/or death within the first 28 days of life

Secondary outcome

• Oxygenation index

• Overall mortality

• Incidence of treatment failure

• Time on intervention drug (intervention drug free days on day 14)

• Vasoactive-inotropic support score

• Need for ECMO

• Ventilator free days on day 28

• Severity of pulmonary hypertension, using laboratory markers and tracheal aspirates for proteomic, metabolomics and biochemical analysis as a marker

• The use of other medication given for pulmonary hypertension during the hospital admission

• The use of pulmonary and/or cardiac medication at discharge and its total duration

• Long-term pulmonary hypertension on echocardiography at 6 and 12 months

• Chronic lung disease

• The development of neurological abnormalities evaluated with ultrasound of the brain

• External validation of sildenafil PKPD model

Study description

Background summary
Infants with CDH will be randomized to receive either iNO or intravenous sildenafil if clinical significant PH is present. The patient can participate in the trial within the first seven days of life. Inhaled NO will be given with a starting dose of 20 ppm. Inhaled nitric oxide will be provided by a tank connected to a neonatal ventilator. Therefore, the study will be open label. Sildenafil with be given intravenously, using a loading dose of 0.4mg/kg in 3 hours, followed by continuous infusion of 1.6mg/kg/day. The patients will be treated according to the standard protocol for patients with CDH, which is implemented in all participating centers according to the revised CDH consortium guidelines. Strict guidelines for cardiovascular support will be used. Echocardiography will be performed to determine eligibility of entry into the study at day 1,and subsequently before study drug administration, on day 14, day 28 (or discharge whichever is sooner) and at follow up at 6 and 12 months. The echocardiographic images will be collected for centralized, blinded analysis of pulmonary artery pressure and cardiac function by 2 investigators. Demographic and neonatal characteristics as well as data on the clinical course and treatment of all patients will be collected in a central database in Rotterdam. Because all patients will be analyzed on the basis of intention-to-treat, data after treatment failure will be collected in a similar way for all included patients.

Study objective
IV sildenafil is superior to iNO for the treatment of pulmonary hypertension in CDH newborns and should be considered as the drug of first choice in the future

Study design
Randomized controlled drug trial, not blinded

Intervention
Sildenafil

>

Study burden and risks
Possible risk of hypotension due to sildenafil.

Extra blood taken and extra echocardiograms made

Contacts

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Eligibility criteria

Age
Newborns
Newborns

Inclusion criteria

Diagnosis of CDH and pulmonary hypertension defined as 2 of the following 4 criteria:

I. Systolic PAP> 2/3 systemic systolic pressure estimated by echocardiography

II. RV dilatation/septal displacement, RV dysfunction +/- LV dysfunction

III. Pre-post ductal SpO2 difference > 10%

IV. OI>20.

Parental informed consent

Children born at or after a gestational age of 34 weeks

Newborns who received a fetal intervention may be included

Exclusion criteria

Severe chromosomal anomaly, like trisomy 18 or trisomy 13, which may imply a decision to stop or not to start life-saving medical treatment Severe cardiac anomaly, expected to need corrective surgery in the first 60 days of life (such as transposition of the great arteries, truncus arteriosus, coarctation aortae or double outlet right ventricle)

Renal anomalies associated with oligohydramnios Severe orthopaedic and skeletal deformities, which are likely to influence thoracic, and / or lung development (such as chest wall deformities and spine anomalies)

Severe anomalies of the central nervous system Patients born in another centre, transported with iNO

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	01-02-2018
Enrollment:	330
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Approved WMO Date:	29-01-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

ID: 50767
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL6796
NTR-old	NTR6982
CCMO	NL60229.078.17
EudraCT	2017-000421-13
OMON	NL-OMON50767

Study results