Newborns with Congenital Diaphragmatic hernia: inhaled Nitric Oxide versus intravenous Sildenafil: ;an international randomized controlled trial

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To determine the most effective drug (iNO or IV sildenafil) for the treatment of PH in newborns with CDH and to reach evidence based dosing of this drug. Subsequently this drug will be added to the international guidelines for the treatment of...

Ethical review	Approved WMO
Status	Completed
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON50767

Source
ToetsingOnline

Brief title
CoDiNOS trial

Condition

- Congenital and hereditary disorders NEC

Synonym
High blood pressure in the lungs in patients with congenital diaphragmatic hernia

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,SSWO en CHD UK Sparks

Intervention

Keyword: Congenital diaphragmatic hernia, Inhaled nitric oxide, Pulmonary hypertension, Sildenafil

Outcome measures

Primary outcome

The primary objective of this study is to determine if there is a difference in OI after 12 hours of treatment between CDH patients treated with iNO versus those treated with intravenous sildenafil. The OI is a calculated value to estimate severity of hypoxemic respiratory failure and is often used as a derivative for the severity of PH in newborns

Secondary outcome

The presence/absence of pulmonary hypertension on day 14 without pulmonary vasodilator therapy and without treatment failure and/or death within the first 28 days of life, overall mortality, treatment failure, time on study drug, need for ECMO, number of ventilator free days at day 28, severity of pulmonary hypertension, laboratory markers and tracheal aspirates for proteomic, metabolomics and biochemical analysis, the use of other medication given for pulmonary hypertension during the hospital admission, the use of pulmonary and/or cardiac medication at discharge, long-term pulmonary hypertension on echocardiography, chronic lung disease.

Study description

Background summary

Congenital diaphragmatic hernia (CDH) is a developmental defect of the diaphragm and both lungs that allows the abdominal content to herniate into the chest. Lung development is impaired in both lungs resulting in pulmonary hypoplasia and abnormal pulmonary vasculature growth, resulting in a variable degree of pulmonary hypertension (PH). CDH occurs in approximately one in 2500 live births and is associated with a reported mortality of approximately 27% in live-born patients. Most children with CDH develop severe cardiorespiratory distress after birth. Initial therapy is focused on *gentle* mechanical ventilation and cardiorespiratory stabilization. Thereafter, surgical repair of the diaphragmatic defect is indicated. PH, severe lung hypoplasia and ventilator-induced lung injury are the most important risk factors for poor outcome in children with CDH.
PH is the cause of considerable morbidity and mortality in 65-75% of newborns with CDH. Elevated pulmonary vascular resistance and abnormal vascular reactivity is due to excessive muscularisation and pulmonary vascular remodeling. PH causes right ventricular dilatation, hypertrophy and dysfunction, which contribute to illness severity including mortality.
Three known cytokine pathways mediate pulmonary artery smooth muscle tone to control PVR: the nitric oxide-cGMP pathway, the endothelin pathway, and the prostacyclin pathway. Pharmacological therapies that target these pathways have been proposed, and are currently used, to treat PH in CDH. However, no prospective studies have resolved the utility, timing and dosage of these therapies while a number are not available in IV form either. As a result there is very limited evidence for the optimal choice of individual drugs in the PH treatment in CDH patients.
At present studies investigating therapies that target endothelin- and prostacyclin pathways are not possible due to the absence of non-enteral forms of these drugs and the lack of data in infants less than three months of age.
Inhaled nitric oxide, iNO, is at present the most commonly administered drug to treat PH in CDH. In non-CDH patients with persistent pulmonary hypertension of the newborn (PPHN) iNO decreases the median duration of mechanical ventilation and the need for extracorporeal membrane oxygenation (ECMO). However, in the one available RCT in patients with CDH INO did not improve, and may even have worsened outcome.
Sildenafil citrate is a selective phosphodiesterase type 5 (PDE5) inhibitor that theoretically acts in concert with NO to increase cGMP-mediated pulmonary vasodilatation. Sildenafil may also augment NO-mediated vasoproliferation. A Cochrane analysis investigated the efficacy and safety of sildenafil in neonates with PPHN without CDH. Three randomized single-center trials were included, in which iNO and ECMO were initially not available. Although the patient numbers are small and not all outcome measures are adequately reported, the meta-analysis showed a significant reduction in mortality in the treated group (20% versus 54% in the placebo group). A RCT comparing sildenafil and placebo in PPHN patients without CDH receiving iNO is currently recruiting

patients (NCT01720524).
For CDH patients, only retrospective data are available. A decrease in pulmonary vascular resistance (PVR) and an increase in cardiac output were found in a small group of oral sildenafil-treated infants with CDH refractory to iNO. Intravenous sildenafil in CDH patients was associated with improved oxygenation index (OI) and reversal of the right-to-left shunt over the patent ductus arteriosus (PDA). As no prospective randomized controlled trials have been carried out to compare iNO and intravenous sildenafil in infants with CDH and PH, a trial to evaluate the effect of these treatment strategies in children with CDH is urgently needed to reach evidence based practice and subsequently implement this in a worldwide standardized postnatal treatment strategy.

Study objective

To determine the most effective drug (iNO or IV sildenafil) for the treatment of PH in newborns with CDH and to reach evidence based dosing of this drug. Subsequently this drug will be added to the international guidelines for the treatment of newborns with CDH to increase survival rate and reduce morbidity including chronic lung disease, and the hospital length of stay. The hypothesis to be tested is: IV sildenafil is superior to iNO for the treatment of PH in CDH newborns and should be considered as the drug of first choice in the future.

Study design

This study is designed as an open label prospective, multicenter, international randomized controlled trial. In this trial, 330 newborns with CDH and pulmonary hypertension will be recruited in a 3-year period, using the established international collaboration within the framework of the CDH EURO CONSORTIUM, an assembly of high volume centers for CDH within Europe.

Intervention

Postnatally, all newborns 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 (published April 2016). Strict guidelines for cardiovascular support will be used. After echocardiographic evaluation on the first day of life, the infant will be randomized to receive either iNO or intravenous sildenafil if clinical significant PH is present. The patient can also be randomized after new echocardiographic evaluation revealing PH within the first seven days of life if PH was not present on day one. The randomization will take place by a web based system using a center specific block randomization. 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. Some centers use integrated systems,

making it impossible to disconnect the iNO tank and replace it with another gas to facilitate a blinded intervention. Therefore, the study will be open label. Sildenafil will be given intravenously, using a loading dose of 0.4mg/kg in 3 hours, followed by continuous infusion of 1.6mg/kg/day. Echocardiography will be performed to determine eligibility of entry into the study at day 1,and subsequently before and after study drug administration, day 7,day 14, day 28 (or discharge whichever is sooner) and at follow up at 3,6 and 12 months. Additional 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. All centers will keep a log book of the number of eligible non-participants, including the reasons for non- participating.

Study burden and risks

The risks involved in the trail are the side effects of both drugs and are expected to be mild. Sildenafil can cause a temporary decrease in blood pressure. This often recovers spontaneously, but can also be treated with medication. Inhaled nitrix oxide can cause methemoglobinemia, which decreases oxygen transport capacity of erythrocytes. This is very rare in the low dose we will be using in our trail. MetHb can be measured in the blood.
At the moment, there is no evidence based treatment of PH in children with CDH, an anomaly with a high morbidity and mortality. Comparing the treatment of first choice with sildenafil, a drug that seems promising in small series, could result in a break trough in the treatment of this severe illness. The side effect of both drugs are limited.
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Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

• Diagnosis of CDH and pulmonary hypertension defined as 2 of the following 4 criteria: , I. PAP> 2/3 systemic 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, • iNO already started for postnatal transport

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-04-2018
Enrollment:	45
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	INOmax / Neophyr
Generic name:	nitric oxide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Revatio
Generic name:	sildenafil
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	07-06-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	27-07-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-07-2020
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

ID: 28811
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2017-000421-13-NL
CCMO	NL60229.078.17