Multi-center, randomized non-inferiority trial of early treatment versus expectative management of patent ductus arteriosus in preterm infants.

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To investigate whether in preterm infants, born at a GA less than 28 completed weeks, with a PDA (diameter >1.5 mm) an expectative management is not inferior to early treatment with regard to the composite of mortality and/or NEC (Bell stage *...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neonatal and perinatal conditions
Study type	Interventional

Summary

ID

NL-OMON47250

Source
ToetsingOnline

Brief title
BeNeDuctus Trial

Condition

- Neonatal and perinatal conditions

Synonym
Patent ductus arteriosus; patent duct

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: ZonMw (projectnummer 843002622)

Intervention

Keyword: Expectative management, Patent ductus arteriosus, Preterm infant, Randomized controlled trial

Outcome measures

Primary outcome

The primary endpoint is the composite of:

- Mortality at a postmenstrual age of <= 36 completed weeks, and/or

- NEC (Bell stage >= IIa) at a postmenstrual age of <= 36 completed weeks, and/or

- BPD, defined as the need for supplemental oxygen need at a postmenstrual age

of 36 completed weeks

Secondary outcome

Secondary endpoints are short term sequela of cardiovascular failure, adverse

effects during the stay in the hospital and long term neurodevelopmental

consequences assessed at a corrected age of 2 years.

Short term sequela of cardiovascular failure

- Hypotension (defined as MABP < gestational age in completed weeks)

- Need for cardiovascular support (volume expansion, inotropes, vasopressors,

corticosteroids et cetera)

- Pulmonary hemorrhage

- Total doses of COXi

- Adverse effects of COXi

- Need for surgical ligation of PDA

Adverse effects during stay in hospital

- BPD at PNA of 28 days

- Mortality at PNA of 28 days and at hospital discharge

- Modes and duration of respiratory support

- Total days of oxygen supplementation

- Incidence of pulmonary air leakage (pneumothorax, pneumomediastinum, pulmonary interstitial emphysema)

- NEC (Bell classification, see Table 3)

- Gastrointestinal bleeding

- Spontaneous intestinal perforation

- Time to full enteral feeding

- Sepsis (positive blood culture and antibiotics)

- ROP, according the international classification (108)

- Length of hospitalization

Long term health and neurodevelopmental outcome at 24 months

- Biometrics (weight, length and head circumference)

- Pediatric examination

- Neurologic examination, according Ariel Tison / Touwen / Hempel

- Cognitive assessment: BSID-III-NL; WPPSI-III-NL; WISC-III-NL

- Behavioral assessment: CBCL / TRF questionnaire

- Motor function: AIMS; Movement ABC 2-NL

- Executive functions: NEPSY-II-NL; BRIEF

- Visuomotor function: BEERY VMI

All primary and secondary outcome parameters are evaluated as part of routine

care in the Netherlands and Belgium.

Study description

Background summary

Much controversy exists about the optimal management of a patent ductus arteriosus (PDA) in preterm infants, especially in those born at a gestational age < 28 weeks or with a birth weight <= 1000 grams. A common understanding is that the actual approach with medical or surgical treatment of a PDA seems not to reduce the risk of major neonatal morbidities. This might be related to the fact that a substantial portion of preterm infants are probably treated unnecessarily, because the PDA might have closed spontaneously without specific interventions. This would imply over-treatment with an increase in iatrogenic risk of adverse effects related to the used drugs and/or surgical ligation. An expectative approach is gaining interest, although convincing evidence is still lacking.

Study objective

To investigate whether in preterm infants, born at a GA less than 28 completed weeks, with a PDA (diameter >1.5 mm) an expectative management is not inferior to early treatment with regard to the composite of mortality and/or NEC (Bell stage * IIa) and/or BPD at a PMA of 36 weeks.

Study design

The design is a multicenter, randomized, non-inferiority study conducted in neonatal intensive care units in the Netherlands and Belgium.

Intervention

Patients randomized to the expectative management arm will not receive any COXi and PDA management in this group can be characterized as *watchful waiting*. This is not a unique approach, since a restrictive approach towards a PDA is increasingly used in many centers worldwide without the observation of an increased risk of neonatal mortality and morbidity, such as severe CLD, IVH, NEC and ROP.
It is essential that neonatal management is similar in both study arms with the exception of the prescription of COXi and echocardiography at the end of the drug course in the medical treatment arm. It is of the upmost importance that NO extra interventions are to be undertaken with the intention to

conservatively prevent or treat a (suspected) PDA in the expectative arm, such as fluid restriction and diuretics for that reason. Moreover, it should be noted that there is insufficient evidence that fluid restriction and/or diuretics are of any benefit in patients with a (suspected) PDA.

When the patient is allocated to the medical treatment arm COX-inhibition is prescribed and started as soon as possible, but no later than 3 hours after the echocardiogram. We prefer to use Ibuprofen (IBU) for COX-inhibition in this study. However, Indomethacin (INDO) can be prescribed for medical ductal closure if this is preferred by a participating center. The medical treatment is considered standard of care in many NICU*s worldwide.

Study burden and risks

All patients in this study are treated according current (inter)national guidelines and local protocols regarding neonatal intensive care management. The administration of ibuprofen or Indomethacin does not pose an extra burden on the patient and is considered routine treatment in preterm infants with a PDA in a majority of neonatal intensive care centers. No extra investigations or interventions are needed in this study. Patients that aren*t treated with COXi are refrained from potential side effects of this drug.
A restrictive approach towards a PDA is increasingly used in many centers worldwide without an concomitant increase in mortality or morbidity related to a PDA. No causal relationship has been proven between a (hemodynamically significant) PDA and the risk of conditions related to pulmonary hyperperfusion (f.e BPD and PH) and/or systemic hypoperfusion (f.e NEC, renal failure and PVL). Many studies have provide us with conflicting data and treatment of a PDA has not resulted in a decreased rate of these morbidities.
The study is group related because a patent ductus arteriosus is a condition that specifically concerns newborn infants, especially preterms, without any known variability related to sex or ethnicity.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

- Gestational age < 28 completed weeks
- PDA diameter > 1.5 mm and ductal (predominantly) left-to-right shunt
- Signed informed consent obtained from parent(s) or representative(s)

Exclusion criteria

- Contraindication for administration of cyclooxygenase-inhibitors (COXi)
- Use of COXi prior to randomization
- Persistent pulmonary hypertension (ductal right-to-left shunt *33% of cardiac cycle)
- Congenital heart defect, other than PDA and/or PFO
- Life-threatening congenital defects
- Chromosomal abnormalities and/or congenital anomalies associated with abnormal neurodevelopmental outcome

Study design

Design

Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-12-2016
Enrollment:	435
Type:	Actual

Ethics review

Approved WMO Date:	22-09-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-11-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-12-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-02-2017
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-02-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-10-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-09-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-07-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
CCMO	NL57885.091.16