Doxapram versus placebo in preterm newborns: a double blinded multicenter randomized controlled trial

A Data Management Plan created using DMPonline

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Project abstract:

Rationale: After preterm birth artificial ventilation is often needed because of underdeveloped lungs and breathing centre. Artificial ventilation is related to impaired outcome and therefore minimized after preterm birth. The newborns' own breathing is supported with air, oxygen and caffeine. Unfortunately, apneas and concomitant oxygen desaturations often persist and potentially affect the brain and its development. Treatment with doxapram provides a potential solution in addition to standard of care for these infants and is increasingly used off-label in European neonatal intensive care units. We hypothesize that treatment with doxapram improves the survival and long term outcome of preterm infants. Objective: The main objective of our trial is to study if doxapram is safe and effective in reducing the composite outcome death and neurodevelopmental impairment at 2 years corrected age Study design: Randomized, double blinded placebo controlled trial, stratified for center and gestational age before or after 26 weeks at birth. Block randomization will be used. Study population: 356 newborn infants admitted to the Neonatal Intensive Care unit, with a gestational age of less than 29 weeks at birth with optimal non-invasive respiratory support and caffeine treatment that still show apnea. Intervention (if applicable): Blinded continuous doxapram (infusion or gastro-enteral) or placebo (glucose 5%) infusion as long as needed. Therapy is down titrated or stopped based on the patients' condition. If endotracheal intubation is needed study drug is stopped. After extubation study drug may be restarted. Switch to gastro-enteral administration is allowed if no iv-access is needed for other reasons. Main study parameters/endpoints: Primary outcome is death or neurodevelopmental delay at the corrected age of 2 years (15% reduction, from 50 to 35%; NNT 7 patients). Secondary outcome includes short term neonatal morbidity, as well as long term follow-up until the age of 5.5 and 8 years. Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Doxapram is already frequently used in our NICUs. Data on safety or long term effectiveness are lacking. Although doxapram seems effective to avoid endotracheal intubation, long term safety and effectiveness needs to be studied. Adverse events and side effects will be monitored. Next to the study drug infusion, there will be no other study-related interventions. All outcome variables are already collected as standard of care. In a subset of patients doxapram plasma levels will be determined to validate the doxapram PK model (blood will only be collected during routine blood sampling, max amount 0.6 ml). The national protocol for preterm birth advices follow-up at 2, 5.5 and 8 years respectively, as in the current study. Additional questionnaires will be used to collect data on the quality of life of patients and their parents.

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Doxapram versus placebo in preterm newborns: a double blinded multicenter randomized controlled trial - Data management ZonMw (English version)

1. General features of the project and data collection

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- The expert is connected to my department or institution

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- Generate new data
- Exclusively quantitative data
- No, I will not be reusing or combining existing data
- Yes, we have reached agreements on the user rights of the data used in the project
- Yes, I will collect the new data in conjunction with other researchers or research groups
- Yes, clear arrangements have been made regarding data management and intellectual property through a consortium agreement

The consortium agreement is in a final draft stage. Clear arrangements within the consortium and with all sites will be made

- Yes (please specify)

The total number of patients that will be included in the trial is 356. Most data include background and clinical characteristics and outcome data. THe included patients will be followed-up until the age of 8 years where possible.

- Data documentation
- Several versions of processed data
- Raw data
- Yes, I will make use of my institution's standard facilities for storage and backup of my data

Data will be collected via an Openclinica e-crf and is stored on the server of the Erasmus MC

2. Legislation (including privacy)

- Gedragscode Goed gebruik van lichaamsmateriaal (Code of Conduct for Responsible Use of Human Tissue)
- The Wet Medisch-Wetenschappelijk Onderzoek met Mensen (WMO, or Medical Research (Human Subjects) Act) applies to my project; I will have it reviewed by a Medical Research Ethics Committee. In addition I will comply with the Kwaliteitsborging Mensgebonden Onderzoek (Quality Assurance for Research Involving Human Subjects)
- Yes, I will involve human subjects in my research. I will comply with the Algemene Verordening Gegevensbescherming (AVG)
- Yes, and this informed consent allows for the reuse of data (note that in the Code of Conduct for Medical Research, ‘reuse’ is also referred to as ‘further use’)

The PIF will be evaluated by the Medical Ehtical Board. It contains all neccesary information about the trial. Parents of patients will be informed about the trial and will be provided with written information about the study. Their informed consent will be asked for participation of their child in the trial. A separate consent is asked for future use of the data.

- Yes, the data will be pseudonymised. (please explain how this will be done, and by which organisation) and

All included patients will retrieve a unique studynumber. The site (hospital where the patient is included) will have acces to a confidential list with the names and birth dates of the newborns.

- Yes

3. Making data findable

- No, I have not yet chosen an archive or catalogue/web portal
- No, I have not yet chosen a metadata scheme
- Yes, I will be using the DOI code

4. Making data accessible

- Yes, immediately
- No, there will be access restrictions to my data collection (please explain)

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- Yes, my institution employs internationally available terms of use
- A steering committee, programme committee or project leader will be charged with approving data requests
- The reimbursement of costs, for example in obtaining the data
- The permitted period of use of the data set
- Whether or not the data set may be linked with another data set (for reasons of privacy)
- The sharing of data for commercial purposes, taking into account the provisions of state aid law
- Collaboration in using the data set, including agreements on publication and authorship
- Conditions related to data security

As we still have to draft the terms of use we do not know the exact statements that will be included. Though, the checked statements above will at least be included.

5. Making data interoperable

- Yes (please specify)

Open Clinica will be used as datamanagement system. All data can be extracted in a format readable by other researches.

- Yes, I will select a metadata standard from the list published by Biosharing (please specify)

ATC codes (medication data)
ICD-10 (disease classification)

- Yes, the participants have given their permission for reuse of the data, and the data have been pseudonymised

6. Making data reusable

- I will document the software used in the course of the project (please specify)
- In addition, I will take further quality assurance measures (please specify)
- I will perform quality checks on the data to ensure that they are complete, correct and consistent (please explain)
- I will document the research process (please explain)

A design paper will be written describing the study set up and its procedures. Furthermore, datadictionaries will be made. Within the data management system (OpenClinica) datachecks for completeness (notifications for missing items) and correctness (crosschecks, validations, anwser ranges/boundries) will be built. After data extracting datacleaning will be done according to a datacleaning SOP.

- No
- Yes (please specify)
- Not yet
- Yes, in accordance with VNSU guidelines (please specify the number of years)
- Amount ..... (please elaborate)

The costs for the datamanager will be partly covered by the budget of the trial.

- Yes (please elaborate)

These costs will be coverderd by the department of Pediatrics, division of neonatology.