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Official title: The extremely low gestational age infants' PARAcetamol Study (PARAS)

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The ELGA infants' PARAcetamol Study (PARAS)

The purpose of this randomized, placebo-controlled, double-blind, phase 2, one center clinical trial is to study the efficacy and safety of early (< 96 h) intravenous (iv) paracetamol in prophylactic closure of *ductus arteriosus* in extremely premature (gestational age <28+0 wk) or low birth weight (<1000 g) infants. The infants born extremely preterm before 28 gestational age (ELGA) and infants with extremely low birth weight of <1000 g (ELBW) are a focus of the study, since a small phase 2 study on paracetamol failed to demonstrate contraction of ductus arteriosus.

The primary outcome is the shortening of the ductal closure time. The secondary outcomes include open ductus arteriosus without any traditional PDA therapies, the need for ductal therapies, cardiac ultrasound findings, the duration of any ventilation assist, paracetamol serum levels, and paracetamol side effects. Other secondary outcomes during the first hospitalization include the long term complications of prematurity (moderate-to-severe BPD, intraventricular hemorrhage gr 2-4, moderate to severe necrotizing enterocolitis, ROP needing therapy), other long-term morbidity, and mortality.

Hypothesis:

1. Early, iv paracetamol therapy reduces the ductal closure time in infants born before 28 weeks, including the ELGA or ELBW infants.
2. Early, iv paracetamol therapy have no detectable adverse effects in ELGA infants.
3. The present paracetamol doses do not result in high paracetamol serum levels.
4. Pharmacodynamics of paracetamol is likely to reveal unique features.

Objectives: to study in ELGA infants requiring intensive care

1. efficacy of early, iv paracetamol in randomized, controlled, double-blind clinical trial
2. safety of early, iv paracetamol
3. pharmacokinetics and pharmacodynamics of iv paracetamol

Sample size:

The sample size calculation was based on our previous studies. In a cohort study on ELGA infants' ductal outcomes with or without iv paracetamol medication, the numbers of ELGA infants with given PDA therapies were 29 (23%) in the exposed group, and 90 (54%) in the control group (Juujärvi et al, Acta Paediatrica 2018). As demonstrated in a phase 2 study, the early paracetamol treatment induced the closure of *ductus arteriosus*: the mean (SD) ductal closure age was 177 (338) h in the whole paracetamol group (Härkin et al. J Pediatr 2016). However, in the subgroup of ELGA infants born before 28 gestation weeks (n=14), the mean (SD) ductal closure ages in the paracetamol and placebo groups were 491 (504) h and 858 (719) h, respectively.

In order to detect the reduction of the ductal closure age from 858 h to 177 h, with 0.05 alpha error and 80 % power, at least 18 infants/group were needed. The plan is to recruit at least 40 infants.

1 Permissions and practices

The following permissions for the trial have been given:
- The Finnish Medical Agency (Fimea)
- The attending hospital's regional ethics board

The trial will be reported in the European Clinical Trials Database (EudraCT) and ClinicalTrials.gov registries.

The present trial is conducted by applying the principles of Good Clinical Practice (Fimea directive 2/2012, Clinical trials). The essential changes in the investigation plan will be announced to Fimea according to the Drug act, moment 87a. This will be announced using the European Commission internet form (http://ec.europa.eu/health/documents/eudralex/vol-10/).

The research physician will discuss with all study patients' parents for informed written consent.

2 Methods

Study patients and the exclusion criteria

Premature infants born before 28+0 gestation weeks, or at birth weight less than 1000 g, and postnatal age less than 96 hours, are eligible to this trial.

The exclusion criteria include:

- severe malformation or suspected chromosomal defect
- other very severe life-threatening disease (*e.g.* very severe birth asphyxia or persistent pulmonary hypertension, etc.)
- no consent by the parent

The patient attending to this trial is allowed to have a ventricular septal defect smaller than 3 mm in caliber, but bigger ones are regarded as the exclusion criteria. An open *foramen ovale* is considered physiological in ELGA infants.

Randomization and masking

The computed randomization will be done beforehand by a separately nominated randomization group. Randomization will be done in blocks of four.

As the informed consent is given, the study patient receives a trial number from the list made prior to the entry of the study. The trial number will match with an envelope where has been drawn a leaflet with the patient's study medication group written on it. The study medication will begin immediately; deadline is the postnatal age of 96 hours.

Placebo, 0.45 % saline, is similar to paracetamol, both being clear liquids, so the staff will remain unaware which drug the patient receives. The study drug will be kept and prepared away from the NICU, at the separate ward 55 office, in a locked cabinet. The study drug will be prepared by the research nurse, the pharmacist of the ward, or during nighttime, by a nurse who does not participate in the study patients' treatment in any way.

Intervention

The study patients will be recruited before 96 h postnatal age. After the parental consent, the patient is assigned the study code number, and the study drug is started accordingly. It is continued for altogether 9 days. The ductal outcomes are defined by the attending clinicians.

The masked study drug is either paracetamol 10mg/ml infusion solution, or placebo, half-physiological 0.45% saline. The placebo is chosen in order to avoid the risk of hypernatremia. The first loading dose is 20 mg/kg, and continued 7.5 mg/kg every 6 hours up to 9 days. The total cumulative paracetamol dose will be 282.50 mg/kg that has not been reported to cause side effects in premature infants in the previous pharmacological or clinical studies (Juujarvi et al 2018). The study drug is administered as 15 minutes infusion.

No other paracetamol preparations are allowed to be given during the study drug. After the trial, the paracetamol administration should be limited if possible. Otherwise, two days wash-out period is recommended. All the other medical or other therapies are prescribed by the judgment by the attending physicians. In cases of suspicion of severe side effects or other absolute necessities, the attending physician is allowed to break the study code, and stop the study drug (protocol violation).

The pain therapy needed is accomplished using openly the opioid preparation used normally in the each unit (*e.g*. morphine, fentanyl).

Duration of the drug

The drug treatment continues for nine days. In the following instances, the drug treatment is to be discontinued early:

- If the child no longer requires any respiratory therapy likely causing pain or discomfort, the patency of the ductus arteriosus is evaluated using ultrasound. The closure of ductus arteriosus indicates the discontinuation of the drug.
- If diagnosis of PDA, requiring specific treatment, is made during the drug treatment, consider discontinue the study drug at least 8 hours before a specific PDA treatment.

Primary outcome

The primary outcome is defined as shortening of the ductal closure time. The cardiac ultrasound examinations will be carried out at least before and during the study drug, as well as at the discharge from the NICU.

Secondary outcomes

Secondary outcomes include open ductus arteriosus without any traditional PDA therapies, the need for PDA therapies, the duration of any ventilation assist, paracetamol serum levels, and paracetamol side effects. Other secondary outcomes during the first hospitalization include the long term complications of prematurity (moderate-to-severe BPD, intraventricular hemorrhage gr 2-4, moderate to severe necrotizing enterocolitis, ROP needing therapy), other long-term morbidity, and mortality.

The efficacy of the pain therapy

The pain symptoms are estimated according to the pain scales used in each center. All the given pain medication (opioid) doses are recorded and cumulative doses calculated. All the post-trial paracetamol doses are counted and recorded as well.

3 Safety

Previously, no hepatic or renal failure has been reported using the study drug dosage. In our previous cohort studies and in the trial of preterm infants, no signs of hepatic, or renal insufficiency has been detected in any patient (Juujärvi 2018, Härkin 2016, Härmä 2016, Aikio 2014).

Drug-induced liver damage (hepatotoxicity) results not from paracetamol itself, but from one of its metabolites, N-acetyl-p-benzoquinoneimine (NAPQI). Therefore, in the case of intoxication, the possible symptoms would not manifest immediately after administration, but after a period of time. The hepatic injury can be prevented by using the available antidote, acetyl cysteine. Even the suspicion of paracetamol overdose should be taken seriously, the situation clarified and acetyl cysteine therapy started promptly.

Typical symptoms and signs of the paracetamol intoxication would be:

- During the first 24 hours after the drug administration, nausea, vomiting, weariness, lack of appetite, and sweating may occur
- 24 – 48 hours after the administration, serum bilirubin and liver aminotransferase levels and prothrombin time increase. Diuresis may decrease due to dehydration (vomiting) or renal injury
- 2 to 5 days after the administration the hepatic and renal failure is manifested, usually with metabolic acidosis

Using early acetyl cysteine therapy, started earlier than 16 h after administration, the hepatic failure can be prevented, but if started later, the possible injury may be diminished as well. The intoxication treatment includes effective intravenous fluid therapy in order to attenuate the metabolic acidosis, and the diuresis should be aimed to be more than 1.5 ml/kg/h.

The intravenously administered study drug can cause no harm to study patients' families, nursing staff, or the ward milieu.

Reporting and follow-up of the possible adverse events or adverse effects

All study infants will be observed for any clinical signs of adverse effects of paracetamol, especially hepatic or renal insufficiency. In most study centers, the serum bilirubin levels and diuresis are detected during the study period. In case of exceptionally severe hyperbilirubinemia, an abdominal ultrasound scan will be done. Any suspicion of hepatic or renal failure would be a reason to immediately stop the study drug and examine the serum transaminase levels. Symptoms of hepatic or renal failure are considered as an emergency.

In case of suspicion of severe safety issues associated with the trial, separately nominated safety group will be able to break the study code and interrupt the trial, if necessary.

All adverse events and suspected adverse effects are classified by the possible association to the study drug. The classification scale is: clear – likely – unlikely – not possible. Sudden unexpected severe adverse reactions (SUSAR) are recorded into a special file maintained by the responsible investigator. Of them, death or danger of life are reported to Fimea within 7 days after the incident, others within 15 days. This file is reported to Fimea every year.

Pharmacokinetics and pharmacodynamics

From all study patients, samples will be recovered. These include umbilical cord or EDTA-Plasma (DNA), serum (paracetamol, paracetamol metabolites, and free radicals) and urine (metabolomics, paracetamol metabolites).

4 Research data

From all study infants, an internet-based study file will be filled out. It contains following information:

- Gestational parameters: maternal age and diagnoses, parity, medications during the pregnancy, possible complications, the amount of amnion fluid, cause of premature birth
- Infants: gestational age, gender, birth measurements (weight, length, head circumference), PDA therapies, blood pressures, cerebral and abdominal ultrasound scan reports, pain medication doses, diuresis.
- Laboratory values: transaminase, bilirubin and creatinine values if taken
- Diagnoses: PDA, BPD, ICH, NEC, ROP

All the research data is confidential. The whole study personnel is bound to secrecy. The data will be collected to specified files stored into the hospital datasets of the responsible investigator's affiliation. The study registry has been reported to Finnish Data Protection Ombudsman's Office.
The study results will be published in international medical series and theses.

Quality control

A separate monitoring group will be nominated to follow the quality and justification of the methods used, and fulfillment of the study patients' rights and their well-being. We propose that no interim analysis is planned unless excess of adverse effects are observed.

5 Long-term follow-up

The long-term follow-up trial is planned to be accomplished at the 2 to 3 years age, and at 7 years age, including developmental and cardiac examinations as well as parental questionnaire.

6 Statistical analyses

Clinical trial data will be analyzed based on the intention-to-treat principles. The data analysis software will be SPSS. Student's t-test, Chi squared test, and regression analyses will be used as appropriate.

7 Timetable estimation

2017-2018: permissions
2018-2020: recruitment of the patients
2020-2021: data analysis and reporting.