The effect of antenatal acetaminophen administration on breathing effort of premature infants at birth: a pilot study

Published: 15-12-2022
Last updated: 30-01-2025

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Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON53465

Source
ToetsingOnline

Brief title
AIR study

Condition

- Other condition

Synonym
Prematurity, preterm birth

Health condition

Perinatale transitie, ademhaling bij geboorte

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: LUMC

Intervention

Keyword: Breathing, Neonatology, Paracetamol, Resuscitation

Outcome measures

Primary outcome

The primary study outcome is the feasibility, expressed as the success rate, n (%), of pregnant women in the study receiving acetaminophen/placebo 0.5-2 hours prior to birth.

Non-success are noted when pregnant women;

- deliver after 31 weeks* gestation, but have already received study medication;

- require more than 3 dosages of study medication;

- withdraw their consent after receiving study medication and before delivery.

Secondary outcome

The secondary study outcome is breathing effort, expressed as average minute volume (mL/kg/min, continuous) in the first 1-5 minutes after birth, calculated using measured tidal volume of spontaneous breaths on CPAP (mL/kg/breath, continuous) and respiratory rate independent of respiratory support (breaths/min, continuous), and assessed by a respiratory function monitor used for respiratory support at birth in the LUMC (Advanced Life Diagnostics, Weener, Germany). .

Study description

Background summary

Premature infants (<37 weeks' gestation) struggle to establish independent gas exchange with spontaneous breathing at birth, because of their immature respiratory systems, what puts them at risk for hypoxia. One of the major reasons for prematurity is chorioamnionitis, inflammation of the fetal membranes and amniotic fluid, which produces prostaglandins (inflammatory mediators) that inhibit respiratory drive. As prostaglandins are also produced during hypoxia and labour, premature infants are often exposed to prostaglandin concentrations that could suppress breathing.

A possible way to stimulate breathing at birth is paracetamol. Paracetamol is an acetanilide derivate with antipyretic and analgesic properties, because it lowers central prostaglandin concentrations (in the brain). Therefore, paracetamol may reduced the inflammatory-mediated respiratory depression and act as a respiratory stimulator. Previous studies reported that paracetamol could lower incidence of apnoea in infants and that premature infants antenatally exposed to paracetamol had improved respiratory function at birth and during intensive care admission. Additionally, paracetamol improved fetal breathing in animal studies.

Paracetamol is safe during pregnancy and has studies with paracetamol administration during labour only reported positive results, i.e. less pain during labour and faster delivery after paracetamol administration (plausibly due to lower pain). Paracetamol likely acts optimally as a respiratory stimulator at birth if administered 0.5-2 hours prior to birth. Therefore, in this study, we will evaluate the feasibility and effect of antenatal paracetamol administration.

Study objective

The primary objective of this study is to evaluate the feasibility of antenatal paracetamol/placebo administration to pregnant women 0.5-2 hours prior to birth. The secondary objective of this study is to compare the effect of antenatal acetaminophen administration to placebo on breathing effort, expressed as minute volume of spontaneous breathing, in the first 1-5 minutes during stabilisation of premature infants at birth.

Study design

We will perform a single centre, triple-blind randomised and placebo controlled pilot study, without placebo and partial blinding.

Intervention

The intervention comprises administration of 1000 mg paracetamol 0.5-2 hours prior to expected birth.
The control group receives placebo with 0.9% NaCl concentrate (physiological saline).

Study burden and risks

Risk: The burden and risks are expected to be equal between the groups based on previous studies and the recommendations of the EMA and FDA. Paracetamol use is allowed during pregnancy by the EMA and FDA in the lowest effective possible dose, shortest possible time and the lowest possible frequency, to which this study adheres by administering a maximum of 3 dosages of 1000 mg acetaminophen intravenously. Paracetamol administration during labour (in the same dosage as our study) has not been associated with adverse outcomes, but only with positive effects consisting of less pain during labour and a faster labour duration. Moreover, in a study with 604 pregnant women using paracetamol in the 3rd trimester, none of the pregnancies had any adverse fetal effects. Furthermore, paracetamol administration already occurs in 20% of all deliveries <31 week*s gestation in the LUMC. As other aspects of care for pregnant women and neonates are according to standard care and follow local and international guidelines, we expect no additional risk of the intervention to standard care.

Burden: We expect the burden of participants to be experienced as light, because the only burden they receive involves: i) reading the participant information form; ii) answering a short questionnaire with 3 questions; iii) and no intake of paracetamol without a doctor's consent just before expected birth.

Benefit and group relatedness: The study population was selected in infants <31 weeks* gestation, because they are often born due to preterm labour and are at risk for both hypoxia and inflammation, which all increase the exposure of the infant to prostaglandins. Paracetamol can improve breathing in premature infants, which decreases the risk of hypoxia and related complications (e.g. potentially injurious and invasive ventilation).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

- Pregnant women expected to deliver between 24+0-29+6 weeks* gestation and admitted to the Leiden University Medical Centre (LUMC).
- Informed consent from caregiver(s)

Exclusion criteria

- Fetuses with congenital anomalies affecting the heart, lungs, kidneys or liver.
- Pregnant women in whom the use of paracetamol is contraindicated for any reason, consisting of: severe renal impairment, severe hepatic impairment, severe active liver disease (including HELLP-syndrome), a known alcohol addiction and a known hypersensitivity to acetaminophen or to any of the excipients in the intravenous formulation.
- Pregnant women that use one of the following medication: probenecid, salicylamide, rifampicin, isoniazid, barbiturates, tricyclic antidepressants, anti-epileptic medication, zidovudine, oral coagulants, metoclopramide, domperidone, colestyramine and imatinib.
- Acetaminophen administration required for standard care within 4 hours prior to birth.

- Decision to give palliative care to the neonate.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	26-09-2023
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Acetaminophen
Generic name:	Paracetamol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	15-12-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	03-04-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-08-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-05-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
EudraCT	EUCTR2022-003415-29-NL
CCMO	NL82714.000.22