RIC-NEC Phase II Feasibility Randomized Controlled Trial: Remote Ischemic Conditioning in Necrotizing Enterocolitis

Published: 04-03-2024
Last updated: 08-04-2024

Primary Endpoint: Feasibility of including patients in the study, randomization and delivery of the intervention. To assess the primary endpoint, we will examine the probability that: (1) a screened patient is eligible; (2) an eligible patient...

Ethical review	Approved WMO
Status	Pending
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON56614

Source
ToetsingOnline

Brief title
RIC NEC

Condition

- Gastrointestinal inflammatory conditions

Synonym
intestinal disease, intestinal inflammation

Research involving
Human

Sponsors and support

Primary sponsor: Hospital for Sick Children
Source(s) of monetary or material Support: Ministerie van OC&W,Trasher Research Fund

Intervention

Keyword: feasibility, NEC, RCT, RIC

Outcome measures

Primary outcome

Primary Endpoint: Feasibility of including patients in the study, randomization and delivery of the intervention.

Secondary outcome

Secondary Endpoints:

1. To determine the acceptability and accurate recordability of NEC outcome measures to calculate sample size for the future Phase III randomized controlled trial.

2. To determine the satisfaction of key trial stakeholders (parents and healthcare workers) with the recruitment process and the intervention to identify facilitators and barriers to participation in a future Phase III trial.

Exploratory Endpoints:

1. Intestinal oxygenation by near-infrared spectroscopy (NIRS) at baseline (before RIC) and continuously for 48 hours after RIC.

Study description

Background summary

Necrotizing enterocolitis (NEC) is an acute and severe intestinal inflammation of the small and/or large intestine. Due to the inflammation, the intestine is

not well supplied with blood (ischemia), and parts of the intestine can die (necrosis). NEC mainly occurs in premature (premature) babies. NEC often requires urgent abdominal surgery. NEC increases the risk of serious additional problems (complications) and death.

The development of NEC is therefore related to reduced oxygen supply to the gut. Recent researchers have shown that inflating and deflating a blood pressure cuff in the arm or leg (similar to taking a blood pressure reading) can protect a distant organ such as the gut during NEC. This treatment is called remote ischemic conditioning (RIC). Many babies can develop serious complications as a result of NEC, and our experiments indicate that RIC can help these babies recover from NEC by improving the oxygen reaching the gut. Previous studies have shown that RIC is safe and well tolerated in 15 small infants with NEC at the Hospital for Sick Children (Toronto, Canada).

Study objective

Primary Endpoint: Feasibility of including patients in the study, randomization and delivery of the intervention.

To assess the primary endpoint, we will examine the probability that:
(1) a screened patient is eligible; (2) an eligible patient consents and is randomized within 24 hours from diagnosis; (3) the RIC maneuver is masked from healthcare workers (responsible nurse, neonatologist, surgeon) and parents/caregivers; (4) a randomized patient receives allocated intervention; (5) a randomized patient receives intervention within 24 hours from NEC diagnosis; (6) a randomized patient is assessed for the NEC-related outcomes which we have selected as potential elements of *primary composite outcome* of the future Phase III trial.

Secondary Endpoints:
1. To determine the acceptability and accurate recordability of NEC outcome measures to calculate sample size for the future Phase III randomized controlled trial.
2. To determine the satisfaction of key trial stakeholders (parents and healthcare workers) with the recruitment process and the intervention to identify facilitators and barriers to participation in a future Phase III trial.

Exploratory Endpoints:
1. Intestinal oxygenation by near-infrared spectroscopy (NIRS) at baseline (before RIC) and continuously for 48 hours after RIC.
2. Intestinal perfusion by abdominal colour doppler ultrasonography at baseline (before RIC) and 48 hours after RIC.

Study design

Phase II multicenter masked feasibility RCT, conducted at 12 academic centers treating preterm neonates with medical necrotizing enterocolitis (NEC) in Canada, United States, United Kingdom, Sweden, and The Netherlands.
We hypothesize that it is feasible to conduct a multicentre randomized trial to evaluate remote ischemic conditioning (RIC) during the management of neonates with medical NEC.
The intervention being tested in this study is RIC, a simple non-invasive physical maneuver that involves the application of brief cycles of ischemia-reperfusion to the neonate*s arm or leg, similar to routine blood pressure measurement. This study will consist of two arms RIC (intervention) and no RIC (control) to compare the RIC intervention to the standard of care.

An infant's participation in this study will last approximately 1 hour per day, on two consecutive days, followed by 2 follow-up assessments, one at 1 month and the other at 3 months after enrollment in the study.
All study activities during this period will be performed during the NICU inpatient or outpatient setting.
The total duration of this study is 2.5 years and the results should be available approximately 6 months after the last patient was recruited.

Intervention

Patients randomized to the intervention arm will receive RIC as well as the standard medical management for NEC. As determined in a previously completed Phase I safety trial (Hospital for Sick Children), RIC will consist of 4 cycles of limb ischemia (5 min) followed by reperfusion (5 min), repeated on two consecutive days. An appropriately sized blood pressure cuff (covering 2/3 of the distance between the shoulder and the elbow) will be applied by a research nurse and/or fellow to an arm (or leg if the arm is not available because of medical reasons such as central line insertion). The systolic blood pressure will be measured before the first RIC cycle using a different cuff of same size (see above) connected to a monitor. During ischemia time, the cuff will be inflated to a pressure of 15 mmHg above the child*s systolic pressure.

Study burden and risks

c. Safety of RIC in infants: RIC appears safe in human premature neonates with NEC, as demonstrated in our Phase I safety and feasibility trial (ClinicalTrials.gov: NCT03860701) by no adverse effects or complications due to RIC. Muscle ischemia could lead to muscle necrosis and rhabdomyolysis. The most severe potential complication of rhabdomyolysis is oliguric acute kidney injury secondary to renal tubules obstruction with myoglobin affecting >50% of the kidneys. RIC may also lead to damage to the limb peripheral nerves. RIC could potentially lead to microhemorrhages (petechiae, ecchymosis, bruising). Also, the presence of an inflated blood pressure cuff over a more extended than usual period - blood pressure measurement - could lead to skin breakdown, especially

in this vulnerable population (neonates). RIC may also cause pain in the limb receiving the RIC stimulus.

Contacts

Public
Hospital for Sick Children

555 University Ave Suite 1526
Toronto, Ontario M5G 1X8
CA
Scientific
Hospital for Sick Children

555 University Ave Suite 1526
Toronto, Ontario M5G 1X8
CA

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

Infants must meet all of the following criteria: (1) Confirmed diagnosis of *medical* NEC based on joint opinion of two attending experts in the field (two neonatologists or one neonatologist and one pediatric surgeon). Therefore, *medical* NEC will be diagnosed when at least two of the following clinical signs and one of the radiological signs will be present: a) Clinical signs (1. abdominal distension; 2. abdominal tenderness; 3. abdominal discoloration; 4. blood in stool); b) Radiological signs (1. pneumatosis; 2. portal venous gas). (2) NEC diagnosis established within the previous 24 hours. (3) Preterm

neonates with gestational age < 33 weeks. (4) Current weight >= 750 g

Exclusion criteria

(1) Indication for surgery in the joint opinion of the attending neonatologist and pediatric surgeon (i.e. surgical NEC). This diagnosis is based on the presence of pneumoperitoneum in the abdominal radiograph and/or failure of medical treatment for NEC; (2) Previous episodes of NEC; (3) Diagnosis of NEC established >24 hours ago; (4) Major congenital heart disease which needs surgical repair; (5)Antecedent limb ischemia/limb thrombotic events, occlusive arterial or venous thrombosis; (6) Associated gastrointestinal anomalies including gastroschisis or congenital diaphragmatic hernia.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2024
Enrollment:	23
Type:	Anticipated

Medical products/devices used

Generic name:	Blood pressure cuff;spygmanometer
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO Date:	04-03-2024
Application type:	First submission
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

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT05279664
CCMO	NL82391.078.23