Nitric Oxide during Cardio Pulmonary Bypass during surgery for congenital heart defects: A Randomised Controlled Trial.

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Primary objective of this trial is to investigate in a double blind randomized controlled trial in children undergoing open heart surgery if NO exposure during CPB reduces the postoperative duration of invasive mechanical ventilation (defined as...

Ethical review	Approved WMO
Status	Completed
Health condition type	Congenital cardiac disorders
Study type	Interventional

Summary

ID

NL-OMON50652

Source
ToetsingOnline

Brief title
Nitric Oxide during Cardio Pulmonary Bypass in CHD

Condition

- Congenital cardiac disorders
- Cardiac and vascular disorders congenital
- Cardiac therapeutic procedures

Synonym
inflammation after congenital heart surgery

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: stichting;fonds;donations

Intervention

Keyword: congenital, heart surgery, inflammation, nitric oxide

Outcome measures

Primary outcome

Length of mechanical ventilation as defined as the duration of respiratory support for all episodes with an endotracheal tube in situ for the first 28 days post randomisation. The outcome will be reported using ventilator free days (VFD). A systematically zero value will be assigned for patient who die to allow important weight to death as the most pejorative outcome.

Secondary outcome

- Incidence of LCOS, need for ECLS, and Mortality
- The length of stay in PICU, hospital length of stay and health care costs
- Levels of systemic inflammatory markers and levels of markers of myocardial injury (in patients with biobanking)
- Platelet function and levels of markers for platelet activation prior, during, and after CPB
- Extent of new and worsened ischemic white matter changes on cerebral MRI.

LCOS is defined as the inability of the myocardium to provide adequate oxygen delivery (DO2) to the tissue. DO2 measurements are not feasible in daily practice, hence accepted surrogate measures are commonly used. For the purpose

of this study, LCOS will be defined

as: blood lactate level greater than 4 mmol/l with a mixed venous saturation level less than 60% in a fully corrected heart (or the SaO2-SvO2 gradient >35% in uncorrected lesion) within the first 48 hours postoperatively and/or high inotrope requirement: Inotrope requirement will be calculated by means of the Vasoactive-Inotrope Score (VIS) (2): VIS = dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min) + 100 x adrenaline dose (mcg/kg/min) + 100 x noradrenaline dose (mcg/kg/min) + 10 x milrinone dose (mcg/kg/min) + 10,000 x vasopressin dose (U/kg/min). A score >=15 indicating low cardiac output syndrome.

Platelet function will be evaluated using the PACT diagnostic tool. PACT is a platelet function test based on flow cytometry. The test determines the reactivity of individual platelets in response to agonist like thrombin, ADP, and thromboxane A2. Reactivity is quantified by determining degranulation, measured as P-selectin expression on the platelet surface, as well as activation of integrin αIIbβ3, determined as binding of fibrinogen to the platelets. It analyses platelet function through standardized flow cytometric assessment of platelet activation markers using nanobodies. Its nanobody-based technology allows for simultaneous assessment of multiple platelet activation pathways.

Study description

Background summary

Epidemiology of Congenital Heart disease - expected impact on the next decades: The incidence of congenital heart disease (CHD) is approximately 1/100 life born children, of which up to 50% at some stage during their life require cardiac surgery to correct the underlying abnormality. In the Netherlands, 1300-1500 children are born each year with CHD. In comparison, in Australia, over 2000 children are born with CHD each year.2 CHD ranks still within the top five causes of infant mortality in most industrialized countries. >75% of infants born with a critical CHD (requiring surgical intervention to survive) survive to one year of age. Over 80% of cardiac surgical procedures require cardiopulmonary bypass (CPB). While the cardiac surgical and intensive care mortality in children following cardiac surgery is low with an 2-5% perioperative death rate dependent on the complexity of the procedure, major postoperative morbidity is common and translates into an increased rate of long-term mortality, morbidity, and disability.

Life-threatening side effects of cardiopulmonary bypass (CPB) and myocardial ischemia during surgery - Excessive systemic inflammation leads to Low Cardiac Output Syndrome (LCOS): Despite major improvements in CPB devices, the exposure of host blood to large artificial organ surfaces combined with myocardial injury during planned myocardial ischaemia, albeit partially protected by cardioplegia, result in a significant systemic inflammatory response of the patient. Indeed, the strong CPB triggered systemic inflammatory syndrome, is responsible for the most serious and potentially life-threatening side effects after heart surgery. CPB, hypoxic-ischemic injury, and the release of damage-associated molecular patterns trigger an inflammatory cascade closely related to sepsis induced systemic inflammatory response syndrome (SIRS). It is characterized by endotoxin release, leukocyte and complement activation, and widespread activation of inflammatory mediators, resulting in endothelial leak, increased oxygen consumption, and organ dysfunction. During CPB applying cardioplegic arrest allows the surgeon to operate on a still heart. While the heart is arrested, myocardial blood flow stops, which results in ischemia and myocardial injury. With restoration of blood circulation at the release of cross-clamping, CPB provides full flows with high oxygen content which can lead to reperfusion injury. Central to the pathophysiology of reperfusion injury is a robust local inflammatory response, children appearing to be particularly susceptible to developing multisystem organ failure as a result of these processes. As a result of the combined effects of direct CPB-related inflammation, myocardial ischemia, and reperfusion, the newly operated on heart is unable to meet the metabolic demands of the body resulting in organ hypoperfusion. This situation is called Low Cardiac Output Syndrome (LCOS), and is commonly defined as increased need for inotropes, increased arterial-venous oxygen extraction, increase in blood lactate levels (metabolic acidosis), decrease in urine output (oliguria) and need for extracorporeal lifes support (ECLS). This CPB triggered systemic inflammatory response leads to acute cardiac dysfunction, with limited reserve to respond to meet the metabolic demands of the vital organs. This situation is defined as Low Cardiac Output Syndrome (LCOS).

Children post bypass commonly develop a low cardiac output syndrome (LCOS) which may be life threatening and represents the major determinant of postoperative outcomes. LCOS manifests with severe organ dysfunction such as respiratory and renal failure, and can lead to organ and brain hypoperfusion, cardiac arrest, and death. The severity of the LOCS is influenced as well by the type of surgery performed, pre-surgical condition of the patient and strongly dependent on non-surgical injury of the heart muscle due to CPB. Several studies have shown that postoperative morbidity and mortality are strongly determined by LCOS (Table 1), which is present in ca. 25-40% of children post CPB in the hours immediately following heart surgery. LCOS may lead to a transient or permanent organ damage, brain ischemia, cardiac arrest and death. Long-term outcome may be affected by acute injury of the developing brain caused by brain ischemia during LCOS.

CPB-related injuries are most pronounced in infants and young children for several reasons, including higher metabolic rate, stronger inflammatory response, higher bypass circuit to patient blood volume, and altered homeostasis. At the same time this is the cardiac surgical group with highest mortality, and with the highest risk of long-term neurological sequelae due to the vulnerability of the immature developing brain. In addition, bypass-induced modulation of inflammatory cytokines can lead to subsequent immunoparalysis enhancing the risk of postoperative invasive infections. Should LCOS become apparent, the level of support that the newly operated on heart receives is increased using fluid boluses and inotropes. Organ replacement such as renal dialysis and prolonged mechanical ventilation may be required. In the most severe cases, the heart is supported mechanically with extracorporeal life support (ECLS). Considering the severe impact of LCOS on patient centred outcomes after surgery for congenital heart disease in children, improved strategies targeting LCOS are urgently needed. Interventions leading to reduced LCOS have a high likelihood to lead to a reduction in the incidence of organ failure, reduce the severe major events such as need for mechanical support of the heart with ECLS, and shorten postoperative ventilation and ICU length of stay.

Current strategies to reduce LCOS are insufficient and lack evidence for benefit:

Steroids. The most common but controversial approach to reduce LOCS is using steroids
given preoperatively to reduce the inflammatory response. There have been few prospective randomized controlled trials of corticosteroids in children undergoing cardiac surgery with conflicting results. Patients randomized to dexamethasone in a relatively small study had significantly less fever, required less supplemental fluid, had greater preservation of renal function and less impairment of oxygenation, and experienced a significantly shortened duration of mechanical ventilation and length of stay in the intensive care unit. In another trial investigating the effect of methylprednisolone 4 h prior

to CPB and in the bypass prime showed that these patients who received two doses of methylprednisolone had significantly less fever, required less fluid, had a significantly reduced oxygen extraction ratio and experienced a trend toward reduced length of stay in the intensive care unit ($p = 0.07$). A recent multicentre study on infants undergoing Norwood surgery reported increased mortality in patients receiving intraoperative steroids, confirming previous concerns about risks and lack of benefit of steroids. The latest adult data suggests that steroids are not beneficial or even could cause more harm than benefit.

Modified Ultra Filtration (MUF). Another prophylactic attempt is using modified ultrafiltration which is used in the vast majority of paediatric cardiac centres. Ultrafiltration removes water, reverses haemodilution and eliminates low-molecular-weight substances, including inflammatory mediators. Ultrafiltration may be used during CPB (i.e., conventional ultrafiltration, CUF) or once CPB is completed (i.e., MUF), with the composition of filtrates being identical and the assertion that a greater amount of fluid and therefore solute may be removed following CPB than can be removed with CUF alone. While some studies have shown a significant beneficial effect of MUF on the postoperative course, others have failed to do so.

The proposed physio

Study objective

Primary objective of this trial is to investigate in a double blind randomized controlled trial in children undergoing open heart surgery if NO exposure during CPB reduces the postoperative duration of invasive mechanical ventilation (defined as ventilator free days within 28 days post randomisation) compared to control.

Secondary Objectives are:
1. To investigate if NO reduces the incidence of low cardiac output syndrome (LCOS),
requirement for extracorporeal life support (ECLS), and 90-day mortality.
2. To investigate if NO reduces the length of PICU stay and health care costs
3. To investigate if NO reduces the inflammatory response following CPB.
4. To investigate if NO reduces the negative effects of CPB on platelet activation and platelet function. (This question is answered within the subgroup of children included at the Utrecht study side)
5. To investigate if NO reduces the ischaemic cerebral damage following congenital heart surgery with CPB. (This question is answered within a subgroup of neonates included at the Utrecht study side that receive a pre- and postoperative MRI as part of their usual care)

Study design

A multi-centre randomised controlled and blinded study in children < 2 years of age undergoing open heart surgery on cardiopulmonary bypass. The study is performed in the following paediatric cardiac centres: Lady Cilento Children*s Hospital Brisbane, Australia;
Royal Children*s Hospital Melbourne, Australia; Starship Children*s Hospital Auckland, New Zealand; Westmead Children`s Hospital Sydney, Australia; Princess Margareth Children`s Hospital Perth, Australia; and Wilhemina Children*s Hospital Utrecht, The Netherlands. The expected duration of the trial is 2-3 years. Participants are randomized in either the intervention arm, where they receive NO during CPB, or to the control arm, where they receive standard care according to the local treatment protocol.

Intervention

Patients allocated to the study intervention arm will receive NO, which will be blended into the fresh gas flow kept at 3L/min for the CPB oxygenator with NO levels maintained at 20 ppm via a NO-A nitric delivery system (EKU Elektronik GmbH, Leiningen, Germany) or Ikaria INOmax DSIR (Ikaria, NJ, USA)). Continuous sampling of NO and NO2 concentration will be undertaken. NO will be started immediately when the patient is on CPB and ceased once coming off CPB. Patients allocated to the Placebo arm will receive standard respiratory gases (oxygen-air mix) during bypass at a flow rate of 3L/min. Partial pressures of CO2 have to be maintained constantly in both study arms as per the institutional practice. Note: If patients require several CPB runs during the same procedure, the treatment will be provided for each run using the same treatment allocation for every run (i.e. patients allocated to study gas arm will receive NO at 20ppm for every run). Subsequent CPB procedures: Patients that were previously enrolled and randomised into the study with surgical procedure performed that required use of CPB will not get re-randomised. Previously enrolled and randomised patients will undergo the same treatment allocation for subsequent surgeries, unless parents opt out. The study perfusionists at each study site have access to the treatment allocation, which will remain blinded for all other study team members.
Perioperative Care: No specific definition of methods of anaesthesia, surgical technique or method on CPB perfusion will be done.
Note: Patients undergoing CPB that are considered by treating physicians (surgeons, anaesthetists, or intensivists) to require inhaled NO can receive iNO at any time of the study (during or after surgery), independently of treatment allocation, delivered as inhalational gas at doses defined by the clinicians (usually 0 to 20ppm).

Study burden and risks

NO administration in the oxygenator of the CPB has been studied in a pilot randomized trial that included almost 200 children who needed heart surgery for congenital anomalies. This trial showed a significant reduction of LCOS when NO

was administered during CPB. This effect was particularly spectacular in neonates where LCOS reduced from 52% to 20%. LCOS is associated with higher morbidity. We expect that participating patients who receive NO benefit by three pathways: (1) NO reduces the strong inflammatory response associated with CPB, (2) NO reduces platelet activation during CPB, and (3) NO reduces myocardial cell apoptosis. By these mechanisms NO administration in the oxygenator of the CPB is expected to reduce morbidity and mortality in children that need heart surgery for congenital heart disease. Potential risks associated with NO delivery are the formation of nitrogen dioxide (NO2) and methaemoglobin (MetHb). Exposure to nitrogen dioxide (NO2) can produce toxicological responses depending on the severity of the concentration and duration of exposure. In the conducted pilot trial, no toxic levels of NO2 or MetHb were detected and adjustment of the NO concentration was not necessary. Extrapulmonary effects of NO2 reported are a blood pressure decrease when exposed to NO2 concentrations > 4 ppm, plasma histamine release, and formation of MetHb. MetHb, an ineffective oxygen carrier, forms when NO binds to oxyhaemoglobin in erythrocytes and is rapidly reduced by methaemoglobin reductase. None of these effects were reported with 20 ppm NO administration during CPB in the pilot study, the trial of Checchia et al, the available adult data, nor in the current trial that already commenced in Australia and New Zealand. NO2 levels and MetHb will be monitored during NO administration.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

- All infants and children < 2 years of age undergoing open heart surgery on CPB
- Elective cardiac surgery and consent of parents/guardian.

Exclusion criteria

- Signs of persistently elevated pulmonary vascular resistance preoperatively requiring iNO or preoperative use of intravenous drugs involved in the NO pathway such as GTN, within 48 hours prior to CPB.- Patient is on ECLS prior to surgery- Concurrent known confirmed bacterial sepsis/septic shock, diagnosed within <48 hours prior to surgery and being actively treated with antibiotics at time of surgery (suspected sepsis treated with antibiotics is not an exclusion criteria unless inotropes are required for treatment of septic shock at time of surgery)- Preoperative acute respiratory distress syndrome requiring HFOV ventilation <48 hours of surgery- Patient requires high doses of vasoactive drugs prior to surgery with an inotrope score >=15 met within 24 hours prior to surgery: Inotrope requirement will be calculated by means of the Vasoactive-Inotrope Score (VIS) (2): VIS = dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min) + 100 x adrenaline dose (mcg/kg/min) + 100 x noradrenaline dose (mcg/kg/min) + 10 x milrinone dose (mcg/kg/min) + 10,000 x vasopressin dose (U/kg/min).- Cardiac arrest within one week (7d) prior to surgery- Emergency cardiac surgery which may preclude obtaining informed consent (defined as acutely required life-saving procedure in a patient unlikely to survive the next hours without the surgery)- Pre-existing methaemoglobinemia (MetHb > 3%)X*t)
Strongly suspected or confirmed COVID-19

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-02-2019
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	INOmax, Neophyr
Generic name:	Nitric oxide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	06-02-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	16-05-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	13-11-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-12-2019

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-04-2020
Application type:	Amendment
Review commission:	METC NedMec

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
Other	ACTRN12617000821392
EudraCT	EUCTR2017-004684-12-NL
CCMO	NL64083.041.18

Study results

Date completed:	31-03-2022
Results posted:	14-08-2023
Actual enrolment:	82

First publication
05-07-2022