Prone and Oscillation Pediatric Clinical Trial

Published: 10-05-2019
Last updated: 12-04-2024

Specific Aims: In children with severe PARDS:1. To compare the effects of prone positioning with supine positioning on ventilator-free days.2. To compare the effects of HFOV with CMV on ventilator-free days.Hypothesis: Children with severe PARDS...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON48534

Source
ToetsingOnline

Brief title
PROSpect

Condition

- Respiratory disorders NEC

Synonym
Paediatric acute respiratory distress syndrome

Research involving
Human

Sponsors and support

Primary sponsor: National Heart, Lung and Blood Institute
Source(s) of monetary or material Support: NHLBI/NIH

Intervention

Keyword: HFOV, PARDS, Prone positioning, RCT

Outcome measures

Primary outcome

Number of 28-ventilator free days

Secondary outcome

Non-pulmonary organ dysfunction

Interaction between effects body positioning and ventilator mode

90-day in-hospital mortality

Duration of mechanical ventilation

Length of PICU stay

Study description

Background summary

Although acute respiratory distress syndrome is a life-threatening and frequent problem experienced by thousands of children each year, little evidence supports best ventilation practices during their critical illness. For over 25 years, pediatric critical care clinicians have debated the risk-benefit ratio of supine versus prone positioning and conventional mechanical ventilation (CMV) versus high-frequency oscillatory ventilation (HFOV).This debate has been recently fueled by the completion of the Pediatric Acute Lung Injury Consensus Conference Group (PALICC) guidelines noting the lack of high quality evidence and the publication of three definitive adult-based studies with acute respiratory distress syndrome (ARDS); specifically, one positive prone positioning trial and two adult ARDS HFOV clinical trials -- one neutral and one likely harmful.5-7 Without pediatric-specific data, the debate of how best to care for children with severe Pediatric Acute Respiratory Distress Syndrome (PARDS) will continue and prevent progress in the field.
Unique maturational differences prevent data generated in adults to be directly applied to children. There are important differences in lung growth and development, immune response and surfactant homeostasis. The scientific premise supporting the potential benefits of prone positioning and HFOV are

well-grounded. Prone positioning augments ventilation (V) and perfusion (Q) matching along the gravitational axis. Improved V/Q matching reduces the need for potentially toxic levels of delivered oxygen and mean airway pressure. HFOV is a mode of ventilation that takes advantage of hysteresis, maintaining the lung open throughout the respiratory cycle, and aims to prevent the injurious effects of volutrauma, atelectrauma and
potentially biotrauma that has been linked to multiple organ dysfunction syndrome (MODS).It is unknown whether prone positioning and/or HFOV provides a benefit in children with severe PARDS as compared to supine positioning and/or a CMV strategy that delivers small tidal volumes.

The purpose of PROSpect (PRone and OScillation PEdiatric Clinical Trial) is to provide evidence to support best ventilation practices in critically ill children with severe PARDS defined per PALICC guidelines. We propose a two-by-two factorial, response-adaptive, randomized controlled clinical trial of supine/prone positioning and CMV/HFOV. Approximately 50 pediatric intensive care units (PICUs), about 2/3 U.S. and 1/3 international, with at least 5 years of experience with prone positioning and HFOV that can provide back-up extracorporeal membrane oxygenation (ECMO) support, will participate. Eligible patients with severe PARDS will be randomized within 48 hours of meeting eligibility criteria and within 4 days of endotracheal intubation to one of four groups: supine/CMV, prone/CMV, supine/HFOV or prone/HFOV. Subjects who fail their assigned positional and/or ventilation therapy for either persistent hypoxemia or hypercapnia may receive a reciprocal therapy while being considered for ECMO cannulation. Our primary outcome is ventilator-free days (VFD) through day 28, where non-survivors receive zero VFD. We have powered this study to detect a clinically
meaningful 2-day improvement in VFD. Up to 1,000 patients will be randomized, stratified by age group (<1; 1-7; 8-17 years) and direct/indirect lung injury. Adaptive randomization will first occur after 400 patients are randomized and have been followed for 28 days, and every 100 patients thereafter. At these randomization update analyses, new allocation probabilities will be computed based on ongoing intention-to-treat trial results, increasing allocation to well performing arms and decreasing allocation to poorly performing arms. PROSpect may close enrollment early for efficacy or futility based on pre-specified stopping rules. Subjects will be monitored for safety and followed until hospital discharge or hospital Day 90, whichever occurs first. Data will be analyzed per intention-to-treat for the primary analyses and per-protocol received for primary, secondary and exploratory analyses.

Study objective

Specific Aims: In children with severe PARDS:
1. To compare the effects of prone positioning with supine positioning on ventilator-free days.
2. To compare the effects of HFOV with CMV on ventilator-free days.
Hypothesis: Children with severe PARDS treated with prone positioning or HFOV

will
demonstrate more VFD.

Secondary: To compare the impact of these interventions on nonpulmonary organ failure-free
days.
Hypothesis: Children with severe PARDS treated with prone positioning or HFOV will
demonstrate more nonpulmonary organ failure-free days.

Exploratory: To explore the interaction effects of prone positioning with HFOV on VFD and
investigate the impact of these interventions on 90-day in-hospital mortality and, among
survivors, the duration of mechanical ventilation, PICU and hospital length of stay.

Study design

2 x 2 factorial randomized controlled adaptive design trial

Intervention

Patients are randomized to one of four groups:
CMV + supine positioning
CMV + prone positioning
HFOV + supine positioning
HFOV + prone positioning

Study burden and risks

The burden is minimal as patients are deeply sedated and/or paralysed and subjected to an intervention that is not uncommon in the intensive care unit. The risk is moderate-to-high, as the study population includes children with severe PARDS and there are inherent risks with both prone positioning and HFOV. However, these risks of these interventions are comparable when a patient would not bein the trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Pediatric patients >=2 weeks of age (>=42 weeks post gestational age) and <18 years of age*Intubated and mechanically ventilated with severe PARDS for <48 hours per PALICC guidelines(chest imaging consistent with acute pulmonary parenchymal disease and OI >=16 or OSI >=12.3). We require two consecutive blood gases meeting severe PARDS criteria (separated by at least 4 hours during which time the clinical team is working to recruit lung volume and optimize the patient*s hemodynamic status per PALICC guidelines).

Exclusion criteria

Perinatal related lung disease
Congenital diaphragmatic hernia or congenital/acquired diaphragm paralysis
Respiratory failure explained by cardiac failure or fluid overload, cyanotic heart disease, cardiomyopathy
Unilateral lung disease*Primary pulmonary hypertension
Status asthmaticus
Obstructive airway disease (e.g.,bronchiolitis or disease states characterized by either: hypercapnia with FiO2< 0.30, and/or evidence of increased resistance visible on the flow -

time scalar, and/or presence of intrinsicPEEP)*Bronchiolitis obliterans
Post Hematopoietic Stem Cell transplant
Post lung transplant
Home ventilator (including noninvasive) or home oxygen dependent
Neuromuscular respiratory failure
Critical airway (e.g., post laryngotracheal surgeryor new tracheostomy) or anatomical obstruction of the lower airway (e.g., mediastinal mass)
Facial surgeryor trauma in previous 15 days
Headtrauma, intracranial bleeding
Unstable spine, femur or pelvic fractures
Acute abdominal process
Obesity (2w-2y: weight-for-height z-score >+3 WHO; >2y BMI z score >+2 WHO)
Received either prone positioning or HFOV with current illness, supported on ECMO
Previously enrolled in current study
Family/medical team not providingfull support (patient treatment considered futile)
Enrolled in any other critical care interventional clinical trial concurrently
Known pregnancy

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-05-2019
Enrollment:	36
Type:	Actual

Ethics review

Approved WMO Date:	10-05-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-02-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	28-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NCT03896763
CCMO	NL68412.042.18