Title: Cerebral oximetry monitoring to detect hypocapnia in newborns undergoing invasive mechanical ventilation: a SafeBoosC-IIIv ancillary study

Sponsor: Copenhagen Trial Unit. Denmark

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Version 1.2

Background

Hypocapnia leads to cerebral vasoconstriction, which may impair cerebral blood flow. An association between hypocapnia and adverse neurodevelopmental outcomes has been described in animal studies (hypocapnia negatively affects the cellular energy metabolism of the brain, resulting in increased apoptosis) (1) and in clinical settings (hypocapnia is associated with periventricular leukomalacia and cerebral palsy in preterm neonates) (2). Avoiding hypocapnia is, therefore, a key element for neuroprotection in newborn infants undergoing invasive mechanical ventilation. High-frequency ventilation (HFV) is used as the first line of rescue ventilation in this specific population. Using continuous end-tidal CO2 (etCO2) monitoring is not possible with high frequency breath rates. In the more immature infants, transcutaneous CO2 (TcpCO2) monitoring comes with a risk of skin injury, especially during the days after birth. Thus, continuous monitoring of pCO2 is challenging in these patients. Additionally, fast improvement in pulmonary compliance and gas exchange after surfactant administration in infants suffering from respiratory distress syndrome, or the use of invasive mechanical ventilation due to non-pulmonary related problems, can lead to inadvertent hyperventilation. In a cohort of 16 very low birth weight infants needing cardiovascular support at La Paz University Hospital in Madrid, we observed that five of them experienced hypocapnic events (defined as arterial pCO2 <35 mmHg or venous/capillary pCO2 < 45) during the first 72 hours from birth, with a total of 14 events across 155 gas samples. Cerebral oximetry monitoring by near infrared spectroscopy (NIRS) can be used as an indirect monitor of changes in pCO2 since changes in pCO2, due to the adjacent cerebral vasoconstriction (during hypocapnia) and vasodilation (during hypercapnia) are well reflected in the cerebral tissue oxygen saturation (rStO2) (3). Thus, NIRS could be particularly useful as a monitoring tool for pCO2 changes when TcpCO2 and etCO2 monitoring is not possible or problematic.

Methodology

Objectives

The primary objective of this SafeBoosC-IIIv ancillary study is to explore the use of cerebral oximetry as a monitoring tool to detect hypocapnic events in newborn infants during the first 72 hours of invasive mechanical ventilation. Second, we aim to explore the correlation between cerebral oxygenation and pCO2.

Study design

This is an ancillary study to the SafeBoosC-IIIv trial of observational and explorative design. Neonates randomised in the SafeBoosC-IIIv trial from centres who agree to participate and provide relevant, additional data, as described below, will be included.

Outcomes

Primary outcome

Number of detected hypocapnic events defined as arterial pCO2 <35 mmHg or venous/capillary pCO2 <45 mmHg during the first 72 hour of starting invasive mechanical ventilation in the two groups.

Secondary outcomes

- Number of detected hypocapnic events during cerebral hypoxia in the cerebral oximetry group.
- Number of blood gasses drawn in the two groups.
- Number of blood gasses drawn during cerebral hypoxia in the cerebral oximetry group.
- Number of changes in minute ventilation during hypocapnia in the two groups.
- Number of episodes of cerebral hypoxia during hypocapnia that was corrected after changing the minute ventilation in the cerebral oximetry group.

Exploratory outcomes

- Correlation between rStO2 and pCO2 at different levels of SpO2.
- Correlation between rStO2 and TcpCO2 at different levels of SpO2.

Patients and interventions

Newborn infants with a gestational age more than or equal to 28+0 assisted with invasive mechanical ventilation during the neonatal period (first 28 days of life) and included in the SafeBoosC-IIIv trial will have continuous cerebral oximetry monitoring (experimental group) or usual care (control group). There are no specific interventions other than cerebral oximetry-based treatment according to the SafeboosC treatment guideline. If rStO2 is predominantly below the hypoxic threshold or drops acutely, the guideline includes considering blood gas sampling and decreasing minute ventilation if PCO2 is below the normal range or low, even in the normal range (4). Thus, there will not be other specifications per protocol regarding the number of gas samples. The clinical team will fill out a bedside paper form prospectively, each time that a gas is collected during the first 72 hours after starting invasive mechanical ventilation (Appendix).

Data collection

When a blood gas is drawn, a member of the clinical team will enter relevant data in the bed-side available data entry form, designed for this ancillary study:

- Type of sample (arterial, venous, capillary)
- Date and time
- pCO2
- rStO2 at time of drawn blood gas (cerebral oximetry group)
- Change in minute volume (MV) (yes/no)
- rStO2 15 minutes after change in MV (cerebral oximetry group)
- Preductal SpO2 (%)
- TcpCO2
- FiO2
- MAP

Data collection should only occur during invasive mechanical ventilation. Thus, if the infant is extubated within 72 hours from initiation of invasive mechanical ventilation, the data collection will end at time of extubation.

Data transfer to eCRF

A separate data entry form will be developed in OpenClinica where the local principal investigator will enter the data from the bed-side paper form. The analyses will be done centrally in Copenhagen, by Copenhagen Trial Unit.Statistical analysis plan. Dichotomous outcomes will be summarized by number and percentages, and continuous outcomes by mean and standard deviation if they are normally distributed or by median and interquartile range if they are non-normally distributed. For outcomes available in both the cerebral oximetry and usual care group, we will assess the intervention effect by analysing dichotomous outcomes using mixed effect logistic regression and continuous outcomes using linear regression. In all regression models, the stratification variable 'site' will be included as random effects while the stratification variables 'gestational age', 'group allocation' and 'surgery' will be included as fixed effect. Effect sizes for dichotomous outcomes will be reported as relative risks with 95% confidence intervals and effect sizes for continuous outcomes will be reported as ratio of means with 95% confidence interval. Since this is an exploratory study with inadequate statistical power to detect meaningful differences in outcomes, we will not report p values. Effect sizes and adjacent confidence intervals should be seen as descriptive and hypothesis generating instead of conclusive. Correlation between rStO2 and pCO2, and rStO2 and TcpCO2 at different SpO2 levels, will be assessed by using Pearson's correlation if data are normally distributed or Spearman rank's if data are not normally distributed. We will also estimate the interindividual and intraindividual variability in rStO2 by using a linear mixed-effect regression model. If participating sites collect continuous data on rStO2, TcpCO2 and SpO2, we will invite these sites to transfer their data to the central trial unit in Copenhagen, for additional analysis on the correlations described above.

Ethics

Sites that participate in this ancillary study must conform with local regulations regarding the requirement of new or updated ethical approval, second to the approval obtained for the SafeBoosCIIIv trial. This study only adds a collection of additional clinical data, and the parents have already signed up for their neonate's participation in the SafeBoosC-IIIv trial.

Timeline

Expected date of registration of the study protocol on clinicaltrials.gov

Once the protocol receives the approval of the Steering Committee, the protocol will be submitted to clinicaltrials.gov and the local Ethics Committee within the following 3 months.

Expected date of manuscript submission

After finishing the recruitment and data collection, the data will be analysed, and the manuscript will be written. The manuscript will be submitted for publication after the primary outcome results of the trial have been published.

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Additional authors

Authorship will follow the criteria defined in the SafeBoosC-IIIv Standard Operation Procedure 'SOP: Substudies and subsequent publications' available on 'safeboosc.eu'. Principal investigators from sites participating in this ancillary study will be invited to coauthor the publication. In order to be listed as co-author, principal investigators must adhere to the Vancouver criteria.

References

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2. Calvert SA, Hoskins EM, Fong KW, Forsyth SC. Etiological factors associated with the development of periventricular leukomalacia. Acta Paediatr Scand. 1987 Mar;76(2):254–9.

3. Martini S, Thewissen L, Austin T, da Costa CS, de Boode WP, Dempsey E, et al. Nearinfrared spectroscopy monitoring of neonatal cerebrovascular reactivity: where are we now? Pediatr Res. 2024 Sep;96(4):884–95.

4. Pellicer A, Greisen G, Benders M, Claris O, Dempsey E, Fumagalli M, et al. The SafeBoosC phase II randomised clinical trial: A treatment guideline for targeted near-

infrared-derived cerebral tissue oxygenation versus standard treatment in extremely preterm infants.

Neonatology. 2013 Sep;104(3):171–8.

Appendix. Patient's form located cot-side.

Cerebral oximetry group. Participant ID:

Type of sample (a/v/c)	Date Time	Indication for drawing blood gas	pCO2	rStO2 at time of drawn gas	Change in MV (yes/no)	rStO2 15 min. after change in MV	Preductal SpO2	TcpCO2	FiO2	MAP

Usual care group. Participant ID:

Type of sample (a/v/c)	Date Time	Indication for drawing blood gas	pCO2	Change in MV (yes/no)	Preductal SpO2	TcpCO2	FiO2	MAP