Protocol title: The effects of treatment guided by cerebral oximetry monitoring on renal outcomes in invasively mechanically ventilated neonates: an ancillary study of the SafeBoosC-IIIv trial

Short Title: SafeBoosC-IIIv renal outcomes

Background

Acute kidney injury (AKI) is a common morbidity in neonates and is often part of a multisystem syndrome that negatively impacts developing organs, resulting in short- and long-term morbidities. A recent meta-analysis by Moraeas et al showed that invasive ventilation is an independent risk factor for the development of AKI (1). Fan et al showed that increased use of invasive mechanical ventilation was a risk factor for the development of AKI (2). In AWAKEN, a multicentric collaborative study, AKI was independently associated with increased morbidities like intraventricular haemorrhage [IVH], prolonged use of invasive respiratory support, length of stay, and an increase in mortality (3).

AKI has also been associated with adverse neurologic and neurodevelopmental outcomes in high-risk neonates. Chen et al assessed associations between AKI and neurodevelopmental outcomes in preterm infants less than 31 weeks of gestational age (4). Long-term follow-up revealed decreased head circumference Z-scores, higher prevalence of microcephaly, and worse neurodevelopmental outcomes in AKI survivors versus controls in unadjusted analyses. Al-Mouqdad et al showed that very low birth weight neonates with AKI in the first 2 weeks of life had abnormal MRI findings at term corrected age: cerebellum signal abnormalities, cerebellar volume reduction, and a high total cerebellum score (5).

The SafeBoosC-IIIv trial aims to assess the benefits and harms of treatment guided by cerebral oximetry monitoring in neonates undergoing invasive mechanical ventilation. Cerebral oximetry monitoring allows clinicians to optimize cerebral blood flow and

oxygenation using the SafeBoosC treatment guideline (6). The guideline's interventions aim to optimize cardiorespiratory support, including blood pressure and perfusion. As shock is a risk factor for the development of AKI, normalizing perfusion may decrease the incidence of AKI in this high-risk population (7, 8).

Methodology

Objective and hypothesis

The objective of this SafeBoosC-IIIv ancillary study is to assess whether treatment guided by cerebral oximetry monitoring in neonates undergoing invasive mechanical ventilation will result in a lower incidence of death, renal replacement therapy (RRT), or AKI up until discharge from the hospital (at a maximum of 90 days after randomisation). We hypothesize that the incidence of death, RRT, or AKI will be lower in the cerebral oximetry group compared to usual care.

Study design

This is an ancillary study to the SafeBoosC-IIIv trial. It will include neonates from centers who agree to participate and provide data on renal outcomes. The additional eligibility criteria will follow those set for the SafeBoosC-IIIv trial (clinicaltrials.gov NCT05907317). Before initiation of recruitment, this protocol will be uploaded to http://zenodo.org. The substudy is registered on clinicaltrials.gov: NCT06926946.

Outcomes

Primary outcome

A composite outcome of death, RRT, or AKI.

We will additionally report and analyze each component of the composite outcome separately.

Secondary outcomes

- Serum creatinine levels (longitudinal measurements)
- Serum creatinine levels (highest measured level)

All outcomes will be assessed up to the point of hospital discharge (at a maximum of 90 days after randomisation).

Outcome definitions for AKI and RRT

AKI will be defined using the neonatal modified KDIGO AKI definition based on serum creatinine levels. This is given below in the table. An infant fulfilling the creatinine AKI stage 1 to 3 will be considered to have AKI (3).

Stage of AKI	Serum creatinine (SCr)
0	No change in serum creatinine or rise <0.3 mg/dL
1	SCr rise ≥0.3 mg/dL within 48 h or SCr rise ≥1.5 to 1.9 x reference SCr* within 7 days
2	SCr rise ≥2 to 2.9 x reference SCr*
3	SCr rise ≥3 x reference SCr * or SCr ≥2.5 mg/dL** or Receipt of dialysis

RRT will be defined as the need for dialysis of any form.

Additional data collected

In addition to the data collected as part of the SafeBoosC-IIIv trial, we will ask the participant centers to collect the following data from clinical records of neonates included in this ancillary study (only routinely collected data) and enter the data in OpenClinica:

- Death before discharge (yes/no)
- RRT before discharge (yes/no)
- Serum creatinine levels, dates, and unit of measures until discharge

For this ancillary study, a separate data entry module will be built in the SafeBoosC-IIIv eCRF. Additional data entries will be based on assessment of clinical records and must be entered in the separate eCRF module at discharge. The additional data will be collected by an unblinded investigator.

Statistical analysis plan

Sample size and power calculations

In a cohort of 2280 invasively mechanically ventilated neonates (median GA 30.6 weeks, IQR 27.4 to 35.7 weeks) across 12 French neonatal intensive care units enrolled in the SEPREVEN trial, mortality was 10.5% (9). In a meta-analysis including more than 98,000 neonates across 201 studies from 45 different countries, the incidence of AKI was 30% (7). Additionally, in a multicenter cohort study from 24 neonatal intensive care units across Australia, Canada, India, and USA including 2022 critically ill neonates, the incidence of AKI in neonates with a gestational age above 29 weeks was 23,5%. In total, 1% of the neonates needed RRT (3).

A total of 1610 infants will be included in the SafeBoosC-IIIv trial. If we assume a 35% incidence of death, RRT, or AKI in the usual care group, we will have to include 850 neonates in this ancillary study to detect a 25% relative risk difference with 80% statistical power, at a 5% alpha-level.

If all neonates are included in this ancillary study, and we assume a 35% incidence of death, RRT, or AKI in the usual care group and a relative risk difference of 25% between the

cerebral oximetry group and the usual care group, we would be able to detect this difference with a power of 97% at an alpha-level of 5%,

Feasibility

Since this ancillary study involves minimal additional data collection than what is already collected for the SafeBoosC-IIIv trial, and since only a little more than 50% of the randomized participants need to be included to obtain sufficient statistical power to detect a relevant difference, we believe this ancillary study is feasible.

Statistical analyses

Data will be analyzed centrally in Copenhagen by the central trial unit. The primary analysis of all outcomes will be based on the intention-to-treat population. Mixed effects logistic regression will be used to analyze the dichotomous outcomes and report the relative risks. In the regression models, 'center' will be included as a random effect, while 'gestational age below or above 34 weeks of postmenstrual age', 'group allocation', and 'surgery' will be included as fixed effect. Longitudinal data will be analyzed using mixed model and continuous data will be analysed using mixed effects linear regression with site as a random effect. Our primary conclusion will be based on the primary outcome, and all remaining results will be considered hypothesis generating. As a sensitivity analysis, we will perform a win-ratio analysis of the primary, composite outcome with the following hierarchy: 1) death, 2) RRT, 3) AKI. For the primary outcome, a p-value less than 0.05 will be considered statistically significant. Dichotomous outcomes will be summarized as numbers, percentages, risk ratios and 95% confidence intervals.

Missing data will be handled as recommended by Jakobsen et al (REF https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-017-0442-1).

Ethics

Centres who participate in this ancillary study must conform with local regulations regarding requirement of new or updated ethical approval, second the approval obtained for the SafeBoosC-IIIv trial. this study only adds collection of additional clinical data, and the parents have already signed for their neonate's participation in the SafeBoosC-IIIv trial, we do not expect that additional ethics approvals are needed.

Timeline

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

March 2025

Expected date of manuscript submission

June 2028

First authors (investigator responsible for the study and publication)

Saudamini Nesargi

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 co-author the publication. In order to be listed as co-author, principal investigators must adhere to the Vancouver criteria. Additionally, Matthew Harer, Mathias Lühr Hansen and Nivedita Kamath, who contributed to the conception and design of this study, will be listed as co-authors as well.

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