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Authors	Hyttel-Sorensen, Simon;Austin, Topun;van Bel, Frank;Benders, Manon;Claris, Olivier;Dempsey, Eugene M.;Fumagalli, Monica;Gluud, Christian;Hagmann, Cornelia;Hellström-Westas, Lena;Lemmers, Petra;Naulaers, Gunnar;van Oeveren, Wim;Pellicer, Adelina;Pichler, Gerhard;Roll, Claudia;Stoy, Lina Saem;Wolf, Martin;Greisen, Gorm
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University College Cork, Ireland
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Clinical use of cerebral oximetry in extremely preterm infants is feasible

Simon Hyttel-Sørensen¹, Topun Austin², Frank van Bel³, Manon Benders³, Olivier Claris⁴, Eugene M. Dempsey⁵, Monica Fumagalli⁶, Christian Gluud⁷, Cornelia Hagmann⁸, Lena Hellström-Westas⁹, Petra Lemmers³, Gunnar Nauelaers¹⁰, Wim van Oeveren¹¹, Adelina Pellicer¹², Gerhard Pichler¹³, Claudia Roll¹⁴, Lina Saem Støy⁷, Martin Wolf¹⁵ & Gorm Greisen¹

ABSTRACT

INTRODUCTION: The research programme Safeguarding the Brains of our smallest Children (SafeBoosC) aims to test the benefits and harms of cerebral near-infrared spectroscopy (NIRS) oximetry in infants born before 28 weeks of gestation. In a phase II trial, infants will be randomised to visible cerebral NIRS oximetry with pre-specified treatment guidelines compared to standard care with blinded NIRS-monitoring. The primary outcome is duration multiplied with the extent outside the normal range of regional tissue oxygen saturation of haemoglobin (rStO₂) of 55 to 85% in percentage hours (burden). This study was a pilot of the Visible Oximetry Group.

MATERIAL AND METHODS: This was an observational study including ten infants.

RESULTS: The median gestational age was 26 weeks + three days, and the median start-up time was 133 minutes after delivery. The median recording time was 69.7 hours, mean rStO₂ was 64.2 ± 4.5%, median burden of hyper- and hypoxia was 30.3% hours (range 2.8-112.3). Clinical staff responded to an out of range value 29 times – only once to values above 85%. In comparison, there were 83 periods of more than ten minutes with an rStO₂ below 55% and four episodes with an rStO₂ above 85%. These periods accounted for 72% of the total hypoxia burden. A total of 18 of the 29 interventions were adjustments of FiO₂ which in 13 of the 18 times resulted in an out-of-range SpO₂. Two infants suffered second-degree burns from the sensor. Five infants died. In all cases, this was unrelated to NIRS monitoring and treatment.

CONCLUSION: The intervention of early cerebral NIRS monitoring proved feasible, but prolonged periods of hypoxia went untreated. Thus, a revision of the treatment guideline and an alarm system is required.

FUNDING: The Elsass Foundation funded the present study.

TRIAL REGISTRATION: Clinicaltrials.gov: NCT01530360.

An extremely preterm infant born before 28 weeks of gestation has about 25% risk of surviving with a severe neurodevelopmental deficit [1]. A likely risk factor is fluctuating cerebral blood flow during the transitional phase in the first days of life [2, 3]. The regional tissue oxygen saturation of haemoglobin (rStO₂) can be esti-

mated in a non-invasive and continuous manner by near-infrared spectroscopy (NIRS) [4]. rStO₂ is primarily correlated with venous saturation [5, 6] – and hence with the balance between cerebral oxygen delivery and oxygen consumption, and is an estimate of cerebral blood flow. SafeBoosC is a research programme aiming to test the benefits and harms of cerebral NIRS oximetry in extremely preterm infants [4, 7].

The research programme Safeguarding the Brains of our smallest Children (SafeBoosC) phase II trial hypothesizes that the burden of cerebral hypo- and hyperoxia can be reduced by 50% with the further aim to reduce brain injury. Infants will be randomised to cerebral NIRS oximetry during the first 72 hours of life and a specific treatment guideline versus blinded NIRS monitoring and standard care. The present study was an observational pilot including ten infants in the experimental group.

MATERIAL AND METHODS

Study design

This was the SafeBoosC pilot study of the experimental arm of the SafeBoosC phase II focusing on the initial 14 days of the planned trial period. It was approved by the local ethics committee (J. no. H-2-2011-069) and conducted at the Copenhagen University Hospital, Rigshospitalet, Denmark. Written informed consent was ob-

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See note

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- 1) Department of Neonatology, Rigshospitalet, Copenhagen, Denmark
- 2) Department of Paediatrics, Rosie Maternity Hospital, Cambridge, United Kingdom
- 3) Department of Neonatology, Wilhelmina Children's Hospital, Utrecht, The Netherlands
- 4) Department of Neonatology, Hospices Civils de Lyon, Lyon, France
- 5) Department of Neonatology, University College Cork, Cork, Ireland
- 6) Department of Maternal and Pediatric Sciences, Università di Milano, Milan, Italy
- 7) Copenhagen Trial Unit, Rigshospitalet, Copenhagen, Denmark
- 8) Department of Maternal and Pediatric Sciences, University Hospital Zurich, Clinic of Neonatology, Zurich, Switzerland
- 9) Department of Neonatology, University Hospital Uppsala, Uppsala, Sweden
- 10) Department of Neonatology, Katholieke Universiteit Leuven, Leuven, Belgium
- 11) Haemoscan B.V, Groningen, The Netherlands
- 12) Department of Neonatology, La Paz University Hospital, Madrid, Spain
- 13) Department of Paediatrics, Medical University of Graz, Graz, Austria
- 14) Department of Neonatology and Paediatric Intensive Care, Vest Children's Hospital Datteln, Germany
- 15) Biomedical Optics Research Laboratory, University Hospital Zurich, Zurich, Switzerland

Extremely preterm infant.



tained from the parents of each child before or shortly after delivery. The study was funded by a grant from the Elsass Foundation.

Patients

Infants born between 24 weeks 0 days of gestation and 27 weeks 6 days of gestation were eligible for enrolment within three hours after birth. An a priori decision not to provide life support was an exclusion criterion.

Enrolment and treatment

Infants were enrolled from September through December 2011. Two NIRS oximeters were used, the INVOS 5100C (Covidien, Boulder, CO, USA) with the Adult SomaSensor and the NONIN EQUANOX 7600 (NONIN, Plymouth, MN, USA) with the 8000CA sensor model.

NIRS monitoring was initiated within three hours of birth and maintained until 72 hours of age. The sensor was repositioned every 4-6 hours to avoid skin burns.

SafeBoosC clinical guidelines

rStO₂ is a composite measure of tissue oxygen saturation across arterial, capillary and venous beds and reflects a balance between cerebral oxygen delivery (CDO₂) and cerebral metabolic rate (CMRO₂). In preterm infants, CMRO₂ is unlikely to vary much, and a change in rStO₂ largely reflects changes in CDO₂. The factors that influence CDO₂ are arterial oxygen saturation, haemoglobin concentration and cerebral blood flow. The treatment guideline is thus focused on interventions that alter one or more of these parameters, e.g. an increase in PaCO₂ and thus a decrease of the vascular resistance in the brain and an increase in cerebral blood flow. The full treatment guideline can be downloaded at the SafeBoosC website [8].

Normal ranges

The target range of rStO₂ in this SafeBoosC pilot was 55-85%. The range was established from unpublished data of NIRS monitoring of 390 infants admitted to the neonatal department in the Wilhelmina Hospital, Utrecht. The range represents the mean rStO₂ ± 2 standard deviations

(SD) and was collected with INVOS with the Adult Soma-Sensor. The hypoxic-ischaemic threshold of rStO₂ in preterm infants is unknown, but data from piglets suggest that it is probably below 50% [9, 10]. The effect of hyperoxia on neurodevelopmental outcome is debated, but to avoid values above mean + 2 SD seems reasonable.

Interventions

The treatment of the infants was at the discretion of the attending medical staff. The research team was not involved. The sensor was only to be moved according to the planned repositioning and not based on rStO₂ values.

Assessment

The nurses documented any interventions motivated by an out of range rStO₂ reading. If available, mean arterial pressure (MABP), arterial haemoglobin oxygen saturation (SpO₂), and transcutaneous partial pressure of CO₂ were collected at the time of intervention, 30 and 60 minutes afterwards, however, at one and four hours for blood transfusion and treatment of a patent ductus arteriosus. Death before discharge and serious adverse events were recorded. All infants were examined with cerebral ultrasound within the first three days and again at 14 days to detect cerebral injury.

The NIRS data were sampled at approximately 0.2 Hz with INVOS and 0.25 Hz with NONIN.

Statistical analysis

Mean rStO₂ and SD of the monitoring period for each infant were calculated. The time with rStO₂ below 55% and above 85% was multiplied by the extent of deviation to provide an estimate of the burden of hypoxia and hyperoxia in %-hours. Normality was tested with Shapiro-Wilk. The agreement of rStO₂ before and after repositioning of the sensor was estimated [11]. The one-hour effect of each intervention on rStO₂ was tested by the paired t test. Statistical testing was done with Analyst-Soft Inc., StatPlus:mac LE, Version 2009.

Trial registration: Clinicaltrials.gov: NCT01530360.

RESULTS

Ten infants (six girls) were enrolled with a median gestational age of 26 weeks and three days (range 24 + 0 to 27 + 3 weeks + days) and a mean birth weight of 816 grams. Antenatal steroids were administered to all mothers. Six of the ten neonates were delivered by Caesarean section.

Cerebral near-infrared spectroscopy data

Cerebral NIRS monitoring was started 133 minutes (range 42-178 minutes) after delivery. The median re-



TABLE 1

Regional tissue oxygen saturation of haemoglobin (rStO₂) characteristics.

Within subject mean rStO ₂ ± standard deviation, %	64.2 ± 4.5
Within subject standard deviation, %	6.8
Mean rStO ₂ of day 1 ± standard deviation, %	64.6 ± 3.8
Mean rStO ₂ of day 2 ± standard deviation, %	64.9 ± 4.9
Mean rStO ₂ of day 3 ± standard deviation, %	63.1 ± 6.0



TABLE 2

Regional tissue oxygen saturation of haemoglobin (rStO₂) spent outside 55-85%. The values are median (range).

Time out of range, hours	7.7 (0.5-19.6)
Time below 55%, hours	6.9 (0.2-19.6)
Time above 85%, hours	0.0 (0-1.3)
Burden of hypoxia, rStO ₂ < 55%, %-hours ^a	30.2 (1.0-112.3)
Burden of hyperoxia, rStO ₂ > 85%, %-hours ^a	0.1 (0-7.6)
Total burden of hyper- and hypoxia, %-hours ^a	30.3 (2.4-112.3)

a) %-hours is the multiplication of duration and extent out of range.

Recording time was 69.7 hours (range 67.2-71.2 hours). 96% of the possible data points were recorded. The within subject rStO₂ was normally distributed ($p = 0.9$). There was no difference in mean rStO₂ between the three days (**Table 1**). The mean rStO₂ of the seven infants monitored with INVOS was $62.3 \pm 3.3\%$ versus $68.3 \pm 4.0\%$ of the three infants monitored with NONIN ($p = 0.03$). The mean difference of rStO₂ before and after sensor repositioning was 1.3% with limits of agreement of -16.6 to +19.3% (**Figure 1**).

Burden of hypo- and hyperoxia

The median burden of hypo- and hyperoxia was 30.3%-hours (**Table 2**). The median burden of hyper- and hypoxia was 37.7%-hours (range 2.8-112.3%-hours) with INVOS and 8.5%-hours (range 2.4-18.4%-hours) with NONIN.

Treatment interventions

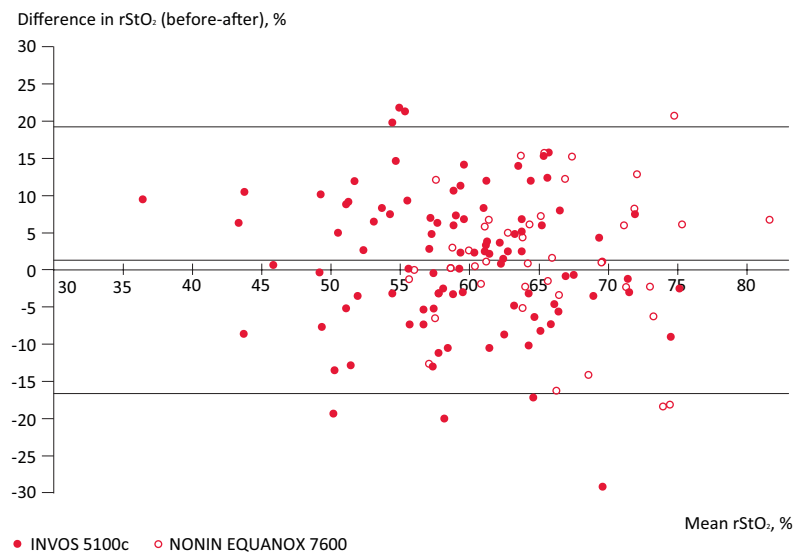
The staff responded to an out-of-range value 29 times. In comparison, there were 83 periods of more than ten consecutive minutes with an rStO₂ below 55% and four episodes with an rStO₂ above 85%. The median duration was 13 minutes. These periods accounted for 72% of the total burden of hypoxia. The longest period was 168 minutes. Only once did the NONIN go below 55% for more than ten minutes, while INVOS never gave values over 85% for ten minutes.

In 15 of the 18 times that the FiO₂ was increased, the rStO₂ was increased 60 minutes afterwards ($p = 0.01$). Unfortunately, the SpO₂ was above the local target range for SpO₂ of 85-92% 13 of the 15 times.



FIGURE 1

Bland-Altman plot of agreement between rStO₂ before and after sensor repositioning. The upper and lower lines represent the 95% limits of agreement. The middle line represents the mean difference.



Dopamine was initiated five times. This was not associated with significant increases in rStO₂ 60 minutes afterwards ($p = 0.1$). Positive end-expiratory pressure was increased, reduced and respiratory frequency decreased once, respectively. One fluid bolus was given and positive inspiratory pressure was reduced twice.

Clinical data

Five of the ten infants died (four to 33 days of age). Three died from necrotising enterocolitis (NEC), one from a catheter-related complication and one from hypoxic respiratory failure. No major cerebral haemorrhages were found. Seven of the ten infants were mechanically ventilated at some point during the first 72 hours, seven received surfactant and seven received prophylactic indomethacin.

Adverse events

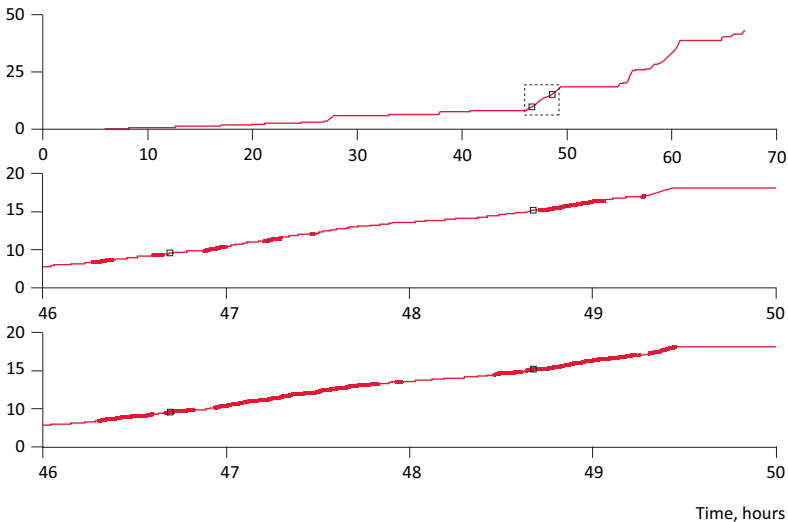
Two infants suffered a burn from the INVOS sensor. One burn evolved into a 4 × 4-mm keloid process. In the second case, the infant died ten days old with a still visible mark on the forehead. There are no data to suggest that NIRS can damage tissue below the skin. In one instance, the tracheal tube disconnected from the ventilator during repositioning of the sensor. Moreover, once the sensor was positioned upside down while still showing rStO₂ values of about 45%.

The infant was otherwise stable and the attending clinician chose to contact the research team and the mistake was corrected. The incident did not affect the treatment of the infant.


FIGURE 2

The accumulated burden of hypoxia during the study period in a single patient. The upper plot shows the whole period with the trial interventions ($\frac{15}{55}$). Middle plot shows the “time-alarm” (—) and lower plot the “burden-alarm” (—) during selected four hours. The alarms alert until the specific conditions are no longer met.

Accumulated burden of hypoxia, %-hours



Case story

A 24-week infant was treated with dopamin to keep the MABP above the “gestational age limit” of 24 mmHg during the first days of life. As dopamin was stopped, the blood pressure dropped to possibly acceptable levels of 24–25 mmHg, but rStO₂ decreased to an rStO₂ of 15%. When dopamin was restarted, MABP increased to 26–27 mmHg and the rStO₂ normalised.

Alarm limits

Two alarm systems with potential to improve timely intervention were explored post-hoc. A “time-alarm”: ten minutes with rStO₂ below 55% and a “burden-alarm”: 25% minutes below during last ten minutes. The “time-alarm” would have alerted during 49% of the total burden of hypoxia, while the “burden-alarm” would have alerted during 77% (**Figure 2**).

DISCUSSION

SafeBoosC is, to our knowledge, the first trial in extremely preterm infants to test the benefit of treatment guided by cerebral NIRS oximetry. This pilot study shows that it was feasible to begin NIRS monitoring within three hours after birth and during the first 72 hours of life in extremely preterm infants in a NICU that had no prior experience with clinical NIRS monitoring. However, we identified potential problems regarding appropriate application of sensors as well as appropriate response to out-of-range values.

The complex intervention of NIRS and the treatment guideline will affect the totality of clinical management of infants depending on various external factors, such as level of experience with NIRS at the specific NICU, local guidelines for treatment of low blood pressure and local SpO₂ ranges. We therefore assumed that a qualitative study could prove valuable for the final planning of the SafeBoosC phase II trial [12].

Our approach has limitations. The study was conducted in one institution only which limits generalisability. Data collection was left to the nursing staff and reduced to a single value at the time of intervention and twice afterwards. This is insufficient to analyse the effects of interventions in detail. Thirdly, when staff records the effects of interventions, it is potentially biased.

The overall mean rStO₂ was $64.2 \pm 4.5\%$. Previously, an rStO₂ of 67–68% in the first three first days of life in infants born before a gestational age 32+0 has been reported [13]. Difference in gestational age could be the explanation. Our data indicate a systematic bias between the NONIN and the INVOS with the used sensors. A systematic comparison with paired measurements on preterm infants should be performed to validate this. The wide limits of agreement between measurements before and after repositioning (Figure 1) are as expected from the literature [13–18]. The upcoming phase II trial will examine the possibility of reducing the burden of cerebral hypo- and hyperoxia. This goal is reachable with NIRS oximeters as long as these are qualitatively accurate. Studying clinical benefit in terms of survival without neurodevelopmental deficit, a phase III trial will, however, depend on the quantitative accuracy of individual oximeters as well as the appropriateness of the intervention thresholds.

The choice of %-hours as primary outcome in the phase II trial is not evidence-based. It is intuitive that both the extent and the duration of hypoxia matter, but their impact on brain injury may not be linear. However, %-hours is the simplest form and is likely to be a relevant marker for the effect of interventions. Data from the phase-II study will be analysed to provide further insight into the association between rStO₂ and brain injury in preterm infants.

As expected, an increasing FiO₂ increased the rStO₂. Unfortunately, the increased FiO₂ often resulted in an out-of-range SpO₂. Large randomised trials have shown that even a five percentage point difference in SpO₂ target range affects the mortality rate [19, 20]. Thus, a change in the trial treatment guideline is warranted. The case story illustrates a steep drop in rStO₂ and presumably cerebral blood flow after cessation of a low-dose dopamin infusion. The 50 percentage point fall in rStO₂ with a fall in MABP of 5–10 mmHg exceeds what would be expected even with complete absence of cerebral

autoregulation. However, the normalisation of rStO₂ when dopamin was started again suggests that a clinically important decrease in CBF did occur. The case illustrates the potential value of this form of “individualised medicine”, i.e. to adapt treatment to the responses in the individual patient.

Our results point to a less than perfect implementation of the treatment guideline. Time limits for intervention were not specified for the staff and it is possible that the clinical judgement was that most episodes out of range would resolve spontaneously. Moreover, the rStO₂ did not show on central monitoring, i.e. the nurses had to be present at the bedside to recognise the low values. Finally, the poor reproducibility of rStO₂, the lack of a well-documented hypoxic-ischaemic threshold and the large spontaneous variation of rStO₂ may have caused the attending staff to disregard the rStO₂ if all other clinical data looked fine.

To intervene every time a highly fluctuating rStO₂ goes below 55% may possibly lead to overtreatment. However, the “time-alarm” would be insufficient for the phase II trial only alerting during 49% of the total burden of hypoxia, whereas the “burden-alarm” would alert during 77% of the total hypoxic burden.

With 700 hours of monitoring, the adverse event rate was reasonable. Side effects of cerebral oximetry are important to acknowledge. For the upcoming phase II trial, adverse events will become a challenge. The control group likely suffers the same expected risks as the experimental group and a higher drop-out rate in the control group might be expected if adverse events are not kept to an absolute minimum. Thus, careful instructions to the attending staff are needed.

Three cases of NEC was more than expected from the unit-specific incidence of 6% in neonates weighing less than 1,500 g. Case reviews did not point to a link between cerebral oximetry or the interventions made and the complications leading to death in any of the cases. The mortality is therefore considered to have occurred by random in this high-risk population. Even so, the observed mortality points to the need for close trial monitoring of the phase II trial.

The SafeBoosC project begs ethical considerations. The adverse device effects appear tolerable, but intervention to change physiological parameters within normal ranges is a new approach. Similarly, physiological parameters outside the normal range may be left untreated if the cerebral oxygenation is normal. However, many of the thresholds that normally guide treatment of these infants are not evidence-based, e.g. thresholds for blood pressure. Cerebral oxygenation is a highly relevant physiological parameter and oximeters have already been approved for clinical use. Diagnostic and monitoring techniques are usually brought into clinical care

without proper trials. We may have a narrow window of opportunity for such a trial.

CONCLUSION

The intervention of the SafeBoosC phase II trial is feasible. However, this pilot study identified issues concerning the NIRS instruments, the treatment guideline and the local implementation that need to be considered in order to ensure optimal execution of the trial intervention.

CORRESPONDENCE: *Simon Hyttel-Sørensen*, Neonatalklinikken, Afsnit 5021, Rigshospitalet, 2100 Copenhagen, Denmark.
E-mail: simonhyttelsorenson@me.com

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CONFLICTS OF INTEREST: none

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