Cerebral Oxygen Saturation to Guide Oxygen Delivery in Preterm Neonates for the Immediate Transition after Birth: A 2-Center Randomized Controlled Pilot Feasibility Trial

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Objective To assess if monitoring of cerebral regional tissue oxygen saturation ($crSO_2$) using near-infrared spectroscopy (NIRS) to guide respiratory and supplemental oxygen support reduces burden of cerebral hypoxia and hyperoxia in preterm neonates during resuscitation after birth.

Study design Preterm neonates <34^{+0} weeks of gestation were included in a prospective randomized controlled pilot feasibility study at 2 tertiary level neonatal intensive care units. In a NIRS-visible group, $crSO_2$ monitoring in addition to pulse oximetry was used to guide respiratory and supplemental oxygen support during the first 15 minutes after birth. In a NIRS-not-visible group, only pulse oximetry was used. The primary outcomes were burden of cerebral hypoxia (<10th percentile) or hyperoxia (>90th percentile) measured in %minutes $crSO_2$ during the first 15 minutes after birth. Secondary outcomes were all cause of mortality and/or cerebral injury and neurologic outcome at term age. Allocation sequence was 1:1 with block-randomization of 30 preterm neonates at each site.

Results In the NIRS-visible group burden of cerebral hypoxia in %minutes, $crSO_2$ was halved, and the relative reduction was 55.4% (95% CI 37.6-73.2%; P = .028). Cerebral hyperoxia was observed in NIRS-visible group in 3 neonates with supplemental oxygen and in NIRS-not-visible group in 2. Cerebral injury rate and neurologic outcome at term age was similar in both groups. Two neonates died in the NIRS-not-visible group and none in the NIRS-visible group. No severe adverse reactions were observed.

Conclusions Reduction of burden of cerebral hypoxia during immediate transition and resuscitation after birth is feasible by $crSO_2$ monitoring to guide respiratory and supplemental oxygen support. *(J Pediatr 2016;170:73-8)*.

Trial registration ClinicalTrials.gov: NCT02017691.

During the immediate transition after birth, the brain needs adequate perfusion and oxygen delivery to maintain cerebral tissue oxygenation and activity.[1,2] If hypoxia or bradycardia occur, cerebral hypoxia-ischemia might cause perinatal cerebral injury including intraventricular hemorrhage (IVH) or periventricular leukomalacia,[3,4] which may lead to subsequent neurodevelopmental morbidity.[4-7]

Pulse-oximetry to monitor arterial oxygen saturation (SpO_2) and heart rate (HR) during this transitional period is widely used, and reference ranges have been established.[8] Nevertheless, monitoring of SpO_2 does not provide information about adequate oxygen delivery to the brain. There is an ongoing discussion about the use of supplemental oxygen during neonatal resuscitation.[9] As the brain is one of the most vulnerable organs of the infant, a noninvasive method to monitor the cerebral oxygenation would be potentially useful. There is an increasing interest in continuous monitoring of cerebral regional tissue oxygen saturation ($crSO_2$) using near-infrared spectroscopy (NIRS) during fetal to neonatal transition.[2] An observational study[10] in preterm neonates with IVH demonstrated increased burden of cerebral hypoxia below the 10th percentile of published reference ranges in term and preterm neonates without any medical support[11] during the immediate transition after birth. Therefore, a reduction of burden of cerebral hypoxia in preterm neonates during immediate transition might be beneficial. On the other hand, there are concerns regarding the potential effects of cerebral hyperoxia, which is associated with increased oxidative stress.[12]

%minutes	Percent $crSO_2$ x minutes
$crSO_2$	Cerebral regional tissue oxygen saturation
FiO_2	Fraction of inspired oxygen
FTOE	Fractional tissue oxygen extraction
HR	Heart rate
IVH	Intraventricular hemorrhage
NIRS	Near-infrared spectroscopy
SpO_2	Arterial oxygen saturation

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Our aim was to examine in preterm neonates the feasibility of reducing the burden of cerebral hypoxia outside the target range of below the 10th percentile of published reference ranges and hyperoxia outside the target range of above the 90th percentile of published reference ranges during immediate transition by $crSO_2$ monitoring in addition to SpO_2 monitoring to guide respiratory and supplemental oxygen support. We hypothesized that respiratory and supplemental oxygen support guided by $crSO_2$ in addition to SpO_2 monitoring will reduce the burden in %minutes (percent $crSO_2$ x minutes) of $crSO_2$ <10th or >90th percentile[11] in preterm neonates during the first 15 minutes after birth.

Methods

A 2-center randomized controlled pilot study (Cerebral Oxygen Saturation to Guide Oxygen Delivery [COSGOD] Trial) was carried out at the Medical University of Graz, Graz, Austria (EK-Nr: 25-592ex12/13) and Royal Alexandra Hospital, Edmonton, Canada (Pro00046517), with institutional ethical approvals. Written parental consent was obtained for all infants: in Graz, only before birth, if possible, 24 hours before birth and in Edmonton, only after birth (deferred consent). Preterm neonates born at $<34^{+0}$ weeks gestation were included. Exclusion criteria were a decision not to provide full life support and congenital malformation.

For this pilot study, the sample size was estimated as 15 neonates in each group at 2 sites resulting in a total number of 60 patients as representative for the target population.[13]

Infants were randomly allocated in 1:1 to either have NIRS-visible (NIRS-visible group) or NIRS-not-visible (NIRS-not-visible group). Allocation was block randomized with 30 neonates at each site. A sealed, opaque envelope containing allocation was opened by a researcher before the birth of an eligible infant. Only the first infant was randomized for multiple births.

Infants randomized into NIRS-visible group had both SpO_2 and $crSO_2$ visible to the clinicians, and infants randomized to NIRS-not-visible group had only SpO_2 visible. After admission to the neonatal intensive care unit, the clinical team was not aware of treatment allocation. In addition, data collector and outcome assessor were both unaware of group allocation.

Immediately after birth, the infant was placed on the resuscitation table and a cerebral NIRS neonatal sensor (INVOS 5100 Cerebral/Somatic Oximeter monitor; Somanetics Corp, Troy, Michigan) was applied to the infant's left forehead and fixed using a cap. A pulse oximetry sensor (IntelliVue MP50 monitor; Philips, Eindhoven, The Netherlands) was applied on the right palm or wrist to monitor preductal SpO_2 and HR. Repositioning of sensors was only allowed after visible displacement.

All variables were stored continuously in a multichannel system "alpha-trace digital MM" (Best Medical Systems, Vienna, Austria) for subsequent analyses. SpO_2 and HR values were stored every second. The sample rate of $crSO_2$ was 0.13 Hz. For further analyses, mean values of SpO_2, HR, and $crSO_2$ for each minute were calculated in each neonate.

At the Edmonton site, delayed cord clamping was routinely performed for 60 seconds with the neonate positioned just below the level of the uterus. At the Graz site, delayed cord clamping was routinely performed for 30 seconds. Resuscitation was performed according to the 2010 Neonatal resuscitation Guidelines of the European Resuscitation Council[14] and the American Heart Association[15] for resuscitation management except for oxygen saturation targeting. If necessary, respiratory support with continuous positive airway pressure and/or positive pressure ventilation was provided using a facemask and the Neopuff Infant Resuscitator (Fisher and Paykel Healthcare, Auckland New Zealand). Default settings were flow 6-8l/min, positive end expiratory pressure 5 mm Hg, peak inflation pressure 25-30 mm Hg, and fraction of inspired oxygen (FiO_2) 30%.

Interventions in Both Groups

SpO_2 and HR monitoring started after birth and lasted until 15 minutes after birth. Both SpO_2 and HR measurements were visible in the NIRS-visible and NIRS-not-visible group (**Figures 1** and **2**; available at www.jpeds.com). According resuscitation guidelines the infants breathing efforts and HR were taken into account and: (1) respiratory support (eg, continuous positive airway pressure or positive pressure ventilation) via face mask was applied or FiO_2 was increased by 10%-20% every 60 seconds[16] if SpO_2 remained <10th percentile[8]; or (2) respiratory support via face mask was reduced/discontinued or FiO_2 was decreased by 10%-20% if SpO_2 remained stable >10th percentile for 60 seconds or if SpO_2 was >90th percentile.[8]

Interventions in NIRS-Visible Group

$crSO_2$ monitoring started immediately after birth for 15 minutes and was visible to the resuscitation team (**Figure 2**). The resuscitation team initially used the SpO_2 to guide medical support. When SpO_2 was between 10th and 90th percentile, the resuscitation team used the $crSO_2$ measurement to provide respiratory support via face mask or FiO_2 was increased by 10%-20% every 60 seconds if $crSO_2$ remained <10th percentile of published reference ranges in term and late preterm neonates.[11] Respiratory support via face mask was decreased/discontinued or FiO_2 was reduced by 10%-20% if $crSO_2$ remained stable >10th percentile for 60 seconds or if $crSO_2$ was >90th percentile of published reference ranges in term and late preterm neonates.[11] The 10th and 90th percentile of $crSO_2$ at each minute was displayed to the resuscitation team (**Table I**; available at www.jpeds.com).

Interventions in NIRS-Not-Visible Group

$crSO_2$ monitoring started after birth for 15 minutes after birth and was not visible to the resuscitation team (**Figure 1**).