Editorial Commentary

The SafeBoosC-III trial and the future of cerebral oximetry-guided interventions in preterm infants—time to pause and reset?

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The complexity of managing extremely preterm babies with limited cardio-respiratory reserve and inability to maintain adequate perfusion to vital organs postnatally, most notably the brain, continues to pose a significant challenge to neonatal practice. The advent of near-infrared spectroscopy (NIRS)-based tissue oximetry in the 1970s (1) held promise for continuously monitoring tissue perfusion noninvasively, enabling caregivers with real-time decision-making capabilities. While it has since found application in adults (2) and in pediatric post-operative cardiac intensive care (3), its ability to detect early signs of physiological abnormalities in neonates to support timely clinical interventions remains to be fully established (4). Despite the introduction of NIRS cerebral oximetry monitoring in preterm infants in the mid-1980s (5), the algorithmic variations among commercially available devices (6), the intersubject variability due to intrinsic patient factors (7), and its high cost has led to uncertainty among neonatologists regarding its clinical utility resulting in its limited adoption across neonatal units (8).

Since routine use of NIRS is not particularly informative, several recent clinical trials (9-11) have aimed to examine the impact of NIRS-guided interventions during specific postnatal periods. These studies have focused on optimizing cerebral tissue oxygenation and its effectiveness in preventing brain injury. Extremely low-birth-weight infants lack cerebral autoregulation, leading to frequent fluctuations in cerebral blood flow (CBF) that are often detected as changes in cerebral tissue oxygenation by NIRS devices. These fluctuations in CBF are well-known to contribute to neonatal brain injuries such as intraventricular hemorrhage (IVH), cerebellar hemorrhage, periventricular leukomalacia, and cerebral atrophy (12). Minimizing the CBF aberrations in the early neonatal period could mechanistically reduce the incidence and severity of brain injury. This has become the premise of studies advocating for timely interventions based on cerebral oxygenation monitoring, such as the 'safeguarding the Brains of Our Smallest Children' (SafeBoosC) trials.

While the SafeBoosC pilot demonstrated the safety and feasibility of NIRS-driven interventions (13), the phase-2 trial (SafeBoosC-II) showed that such interventions could indeed decrease the duration of cerebral hypoxia or hyperoxia by approximately 58% (14). Despite being one of the field's most extensive randomized controlled trials at the time, the SafeBoosC-II trial lacked the power to identify

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disparities in clinical outcomes. A 2-year follow-up study of 83 infants from the SafeBoosC-II showed no significant improvements in neurodevelopment in the experimental group (15). However, encouraged by the successes of the phase 2 trial, the SafeBoosC group designed a large multicenter pragmatic, superiority, open label, randomized, phase 3 clinical trial conducted at 70 sites across seventeen countries (9). This study was designed and powered to assess whether treatment guided by cerebral oximetry when compared to usual care during the first 72 hours after birth in preterm infants with a gestational age of ≤28 weeks, would result in a decreased incidence of death or survival with severe brain injury at 36 weeks post-menstrual age (PMA). A total of 1,601 infants with a gestation of ≤28 weeks at birth underwent randomization, out of which 1,579 (98.6%) were eventually evaluated for primary outcomes. Nonadherence rates were low at 4.7% in the cerebral oximetry group (>14 hours of missing oximetry monitoring data) and 2.5% in the usual care group (who underwent oximetry monitoring), indicating minimal attrition. Death rates were 21.2% in the cerebral oximetry group and 19.8% in the usual care group [relative risk (RR) =1.07; 95% confidence interval (CI): 0.89–1.28]. Severe brain injury occurred in 24.2% of infants in the cerebral oximetry group and 23.6% in the usual care group at 36 weeks PMA (RR =1.02; 95% CI: 0.85–1.21). The combined outcome of death or severe brain injury at 36 weeks PMA was 35.2% for cerebral oximetry and 34% for usual clinical care (RR =1.03; 95% CI: 0.90–1.18; P=0.64). The study found no association between interventions guided by cerebral oximetry monitoring in the first 72 hours after birth and a reduced incidence of death or severe brain injury.

The SafeBoosC-III study is currently the largest and most diverse randomized controlled trial assessing cerebral oximetry-guided interventions in neonates. Very few clinical trials have attempted to use a complex, algorithm-based, multitiered approach to address altered physiological indices to prevent imminent brain injury in preterm infants, a major strength of the study. Despite its thorough execution, the researchers failed to demonstrate the superiority of cerebral oximetry-guided interventions over usual care in terms of reducing death or minimizing severe brain injuries. The lack of improved outcomes in the study arm could be attributed to several factors intrinsic to the study's pragmatic design, where there is potential for significant clinical practice variations across institutions beyond the scope of the study protocol. Additionally, the selection of cerebral oximetry thresholds could have been suboptimal to accurately reflect physiological derangements that portend brain injuries, or the type and timing of interventions did not adequately address the underlying pathophysiology. The primary brain pathologies studied in SafeBoosC-III are also highly influenced by antenatal management practices, ensuring the uniformity of which was beyond the control of the investigators. For example, antenatal steroids, the presence of maternal chorioamnionitis, mode of delivery, use of magnesium sulfate, and placental abnormalities leading to hypoxia ischemia have all been shown to influence the incidence of neonatal cerebral injuries (16,17). However, data on these crucial contributive variables was not provided. Delivery room resuscitation, intubation, and surfactant administration are also known to significantly affect the CBF (18,19). A considerable number of infants in both groups were born very premature (approximately 45% in each group were born at <26 weeks' gestation) and needed surfactant administration and mechanical ventilation. It remains unclear whether these common early neonatal interventions could have influenced the eventual outcome, regardless of the later administered NIRS-guided interventions, which typically started at about ~3 hours after birth (interquartile range 2–4 hours).

As mentioned in the study, restricting cerebral oximetry monitoring to the first 72 hours after birth misses critical episodes beyond this timeframe. While the first 3 days are crucial for identifying the majority of IVH in premature infants (20), the longitudinal risk of brain injury due to oxygen fluctuations and blood flow variations extends well beyond this period, particularly in infants born on the cusp of viability. Moreover, a multitude of postnatal interventions are known to impact cerebral injury. Approaches such as sedation, midline positioning, minimal stimulation, and aggressive management of ventricular dilatation are considered neuroprotective, while frequent painful procedures, aggressive suctioning, and early administration of postnatal steroids have been identified to exacerbate brain injury (21,22). Any of the above factors could have influenced the primary outcome of this study. The complex pathogenesis of neonatal brain injuries and limitations in intervention strategies could explain why interventions on cerebral oxygenation alone may not improve clinical outcomes in neonates. A post hoc analysis of 114 of the 133 surviving infants from the SafeBoosC-II trial studied the associations between the burden of early cerebral hypoxia and the 2-year neurodevelopmental outcomes. The infants were stratified by the burden of hypoxia into low burden

(if the infants fell within the first three quartiles) and high burden (if the infants were within the fourth quartile). Anticipatedly, more infants from the control group fell into the high-burden group. Despite that, the analysis found no statistical associations between hypoxia burden and quantitative neurodevelopment assessments. Although not statistically significant, infants in the high burden of hypoxia group have a higher rate of cerebral palsy [odds ratio (OR) =2.14; 95% CI: 0.33–13.78] and severe developmental impairment (OR =4.74; 95% CI: 0.74–30.49). The study authors speculated that the effects of cerebral hypoxia may diminish with age due to multifactorial etiology impacting long-term outcomes in preterm infants. However, they did not rule out the possibility of clinically relevant associations, citing their study's small sample size and wide confidence intervals (23). Therefore, although NIRS is recognized as a valuable tool for tracking hypoxia trends, benefits in neurodevelopmental outcomes of NIRS-guided therapies remain to be realized. The long-term follow-up data of large cohorts enrolled in the SafeBoosC-III and the 'cerebral regional tissue oxygen saturation to guide oxygen delivery in preterm neonates during immediate transition after birth' (COSGOD-III) trials are eagerly awaited.

Achieving consistency in practice across 70 centers spanning seventeen countries presents a formidable challenge. To address this problem, the authors developed and implemented a multilingual web-based training program covering various aspects, including an introduction to SafeBoosC-III and its protocol, cerebral NIRS monitoring, treatment guidelines, cranial ultrasound imaging, brain injury diagnosis, and monitoring of good clinical practices (24). Despite their efforts, only 24% of nurses and 29% of neonatologists were certified by the start of randomization (9) (*Fig. S2*). Recognizing the potential for practice variations, the authors conducted a random-effects meta-analysis to examine outcome differences among individual centers, focusing on primary outcomes within the intention-to-treat population. While no significant disparities were found between the oximetry group and the usual care group across the 66 centers analyzed, the limited sample size of individual centers may have impacted the ability to detect significance (9) (*Fig. S3*).

Although multicenter randomized trials are known to decrease bias, the SafeBoosC-III trial highlights the complexity of achieving homogeneity in practice, which could affect the outcomes. To highlight, centers in this study have used multiple cerebral oximetry devices despite evidence that each device has variability in its measures of regional oxygen saturations. To their credit, the investigators showed diligence in stratifying the hypoxic threshold for intervention (corresponding to 55% on INVOS^{TM} small adult sensor) across 13 different combinations of devices and sensors used in the participating institutions by utilizing a previously validated blood-lipid phantom method (25). As the authors have rightly enumerated, one significant weakness of the study is the failure to collect the cerebral oxygenation monitoring data, making it uncertain whether the employed interventions resulted in the normalization of cerebral oxygenation as was demonstrated in the SafeBoosC-II study. Furthermore, there was a need to elucidate better the frequency, type, and effectiveness of the interventions employed across participating centers.

As highlighted by this study, a fundamental issue with cerebral oximetry monitoring is whether early interventions guided solely by cerebral oximetry can effectively reduce mortality or severe brain injury.

While cerebral oximetry might pick up alterations in physiological parameters, these variations in physiological indices may not necessarily be pathological or are not sensitive or specific enough to predict ongoing/impending pathology. For example, multiple observational studies have documented lower cerebral oxygen saturations following IVH but there are no studies to date which establish a causal relationship between cerebral tissue hypoxia and IVH. Furthermore, the NIRS-guided interventions to decrease hypoxia burden have not resulted in reducing the incidence of IVH and other cerebral injuries calling into question its overall clinical utility (9,10). Finally, it is possible that considering the myriad of variables that impact cerebral injury, and the potential for differences in the implementation of interventions across centers the power calculations could have been ambitious.

Like SafeBoosC-III, another recently published multicenter phase III trial—the COSGOD-III (10), which investigated the use of NIRS in directing delivery room resuscitation and transition during the first fifteen minutes of life also failed to demonstrate an advantage in improving survival without cerebral injury in infants born ≤32 weeks' gestation. The lack of benefit in both these studies suggests the limitations of cerebral oximetry-guided interventions, the inability to control a myriad of confounding contributors in clinical trials, and the longitudinal nature of insults leading to brain injury in prematurely born infants. Given the individual constraints of these recently published studies, whether NIRS-based interventions merit continued

use in clinical practice remains unanswered.

In summary, this large multicenter randomized control trial attempted a multipronged approach to restitute altered cerebral oximetry to prevent death or brain injury in extremely preterm infants. Despite developing a complex algorithm-based intervention strategy, the investigators could not show differences in primary or significant secondary outcomes. While the long-term neurologic outcomes of the trial participants from SafeBoosC-III and COSGOD-III trials are still awaited, the current study calls into question whether cerebral oximetry-guided interventions in this manner can prevent brain injury. Given the contribution of prenatal factors to brain injury, the complex pathophysiology and longitudinal nature of their evolution, and the unproven efficacy of various intervention modalities, the challenges of using cerebral oximetry to prevent brain injuries in preterm infants appear difficult to surmount. As we look to the future of research with NIRS-based interventions in the neonatal intensive care unit (NICU), a more effective approach could involve stringent exclusion criteria, detailed intervention protocols, and standardized methods to control for other influential variables. Another approach could be a multi-arm study that compares the effectiveness of clinical interventions at various thresholds of cerebral oxygen saturations instead of a single value defining cerebral hypoxia. Such explanatory study designs could better demonstrate whether cerebral oximetry yields clinical benefits. While NIRS thresholds that are applicable to cohorts of preterm infants can be useful, it is possible that individual trends and degree of deviations from baseline are potentially more informative of physiological derangements and impending pathology. Hence, focusing on specific clinical scenarios, such as using NIRS during post-natal resuscitation or monitoring oxygen demands in conditions like sepsis, necrotizing enterocolitis, and hemodynamically significant ductus arteriosus, also offers promise. These situations are known to impact CBF, making them suitable for investigating the utility of monitoring the cerebral oximetry trends in individual patients. Exploring and validating cerebral oximetry thresholds or deviation limits for individual infants is likely more beneficial than setting rigid intervention thresholds for low and high cerebral oxygen saturations across populations. Longitudinal monitoring of cerebral oximetry alongside assessment of other physiological indices might also represent a way forward. While the investigators must be commended for the sheer effort on this complex clinical trial, the results lend a pause to future studies of this nature.

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Footnote

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