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EDITORIAL

The clinical usefulness of cerebral oximetry

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In this issue of the journal we find further evidence in support of the clinical usefulness of monitoring of cerebral oxygenation by near-infrared spectroscopy (NIRS) [1]. Cerebral hypoxia as assessed by NIRS and detected in the first 72 h of life was found to be associated with death or neurodevelopmental impairment at 2 years of age in a group of preterm infants less than 32 weeks [1]. This association in Katheria's data was greatest in the group of infants born at less than 28 weeks gestation, where those with adverse outcome had a prolonged duration of hypoxia (7.4% versus 3.4%). Unfortunately, no further analysis of thresholds, neither in duration of hypoxia, nor in degree, is provided. It would be interesting to understand the dose-response, in particular by testing values of hypoxic thresholds other than 67%.

This study raises two important questions: (1) can cerebral hypoxia data be used to predict outcome and (2) can the incorporation of cerebral oxygenation monitoring in intensive care improve clinical outcome in preterm infants?

This study suggests that cerebral oximetry data may be used for outcome prediction. In some instances this may affect decision making and result in redirection of care. Evidence of severe brain injury from cranial ultrasound (and MRI) findings is typically used for diagnosis and prognosis, and the decision-making process may be significantly facilitated by the addition of another readily available bedside parameter such as cerebral oximetry.

In the present study, however, the authors chose not to adjust for the presence of severe brain hemorrhage on cerebral ultrasound. This may be fair from a causal inference point of view since cerebral hypoxia may lead to severe hemorrhage. Therefore, adjusting for cerebral hemorrhage might erroneously mask some of the causal link. However, for the purpose of prediction, omitting this adjustment might result in overestimation of the value of cerebral hypoxia *over-and-above* what the clinician would know already from brain imaging.

Furthermore, studies of predictive value are needed that analyze combinations of indicators and include an analysis of the information that was available at particular points of time in the clinical course. When it comes to the question of tailoring the follow-up program after discharge, it is likely that the clinical state at discharge, the results of late brain imaging and/or neuropsychological testing may overrule the predictive value of events that occurred early in the neonatal course.

Then, can the continuous availability of a measure of cerebral oxygenation be used to improve clinical outcomes? This question can be divided into two components.

The first one is: can the burden of cerebral hypoxia in extremely preterm infants be reduced? We believe so, as shown in the SafeBoosC-II trial which found a more than 50% reduction [2] in the 'burden' of cerebral hypoxia when incorporating a physiology-based guideline for intervention [3]. The interventions consisted of adjustment of the everyday support of ventilation and circulation common in all NICUs (Fig. 1, unpublished data). As it was a relatively large, multicenter trial it is likely that this effect may be reproduced wherever such a care model is applied.

The second one is more challenging: can a reduction in cerebral hypoxia actually improve clinical outcomes?

Near-infrared light penetrates into tissue and can therefore be used to probe tissues a few centimeters below the skin. The newborn brain is an ideal target for exploration, as it sits at a depth of about 5 mm under the skin, with a predictable anatomy. So, the number that is available at the bedside does mainly represent the oxygenation of the brain,

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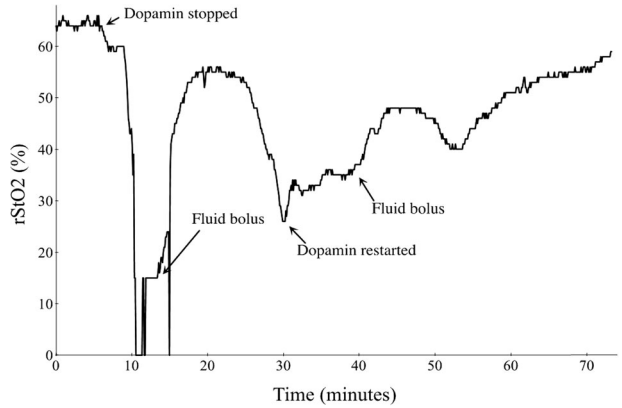

Fig. 1 A tracing of cerebral oxygenation recorded during the SafeBoosC pilot study. An extremely preterm infant was clinically stable during the first day of life and dopamine infusion was stopped. Within a few minutes (*X*-axis), cerebral oxygenation (rStO2, *Y*-axis) dropped to unmeasurable values. After a bolus of saline, restart of dopamine, and another bolus of saline, rStO2 gradually recovered to the initial range. The question was—and is—does the instantaneous access to rStO2 values (and the tracing) allow tailoring ventilation and circulation management to improve clinical outcomes?.

and to a much lesser extent that of superficial tissues. This is a much better situation than in adult patients.

It is common understanding that hypoxia is a threat to the brain. Brain tissue has a high metabolic rate and small stores of substrates for anaerobic metabolism. Acute hypoxia/ischemia, e.g. due to cardiac arrest, leads to irreversible brain injury within minutes. Therefore, a common goal of life-supporting care of all kinds of patients is to ensure equate oxygenation of tissues—not least the brain—at all times by supporting ventilation and circulation as deemed necessary by conventional monitoring of EKG, blood pressure, and arterial oxygen saturation. And here is the obvious slot for cerebral oximetry.

The immature brain, however, has lower metabolic rates, around 40 micromol O2/100 g/min [4], compared to two to three times more in adults, can tolerate much lower perfusion pressures [5], and its microvasculature is adapted to the lower fetal levels of arterial oxygen saturation [6]—at least for some time after birth. Although neurodevelopmental deficits are common in preterm infants, particularly in extremely preterm infants, and although some of these deficits are due to frank brain injury, a significant proportion of deficits are unexplained by routine brain imaging [7]. Furthermore, many other complications to preterm birth, such as inflammation, nutritional insufficiency, and abnormal sensory inputs may contribute, and it has been proposed that hypoxia/ischemia is not a significant contributor to the overall burden of neurodevelopmental deficits in this vulnerable population [8].

A further complication is that not all individual commercial devices give the same results. This means that results from one study with one device may not be reproduced when using another device or even another type of sensor. This is particularly problematic if a hypoxic threshold (such as 67% used in Katheria's study) is used to indicate the need for intervention. When cerebral oximetry is used during anesthesia and surgery, it is customary to operate with relative values, e.g. accepting drops in cerebral oxygenation up to 20% from the level established when the patient was awake. In the care of preterm infants during the first days of life, however, such an individual reference value is rarely available.

In general it is difficult to get precise information on the technical details behind the numbers provided by any given device, and many factors influence the readings, such as the choice of wavelengths, the arrangement of light source(s) and detector(s), the absorption coefficients used for the algorithms, as well as assumptions about the scatter of light in tissue. Some devices have been calibrated in adult volunteers breathing oxygen-nitrogen mixes, but the relevance of this for extremely preterm infants with fluctuating pCO2 is doubtful. Fortunately, an ISO standard is forthcoming that will allow device manufacturers to demonstrate the characteristics of their devices in highly reproducible phantoms that are tailored to match the physics of the newborn infant head.

So, are we ready for the routine use of cerebral oximetry in the NICU?

Probably not. Indeed, although better technology is coming, no quantum leaps are expected. Health care personnel availability is limited in busy NICUs and the benefit of monitoring cerebral oximetry may depend as much on the agility of the clinical staff as on the device itself.

Therefore, a large, pragmatic randomized clinical trial is underway, using any kind of commercial device with a calibrated hypoxic action threshold [9], to constitute a generic trial. Crowd funding has been necessary, and the collected dataset is minimal to make the trial pragmatic. The primary outcome is survival without major brain injury at 36 weeks postmenstrual age. A total of 1600 babies will be randomized across more than 50 NICUs http://www.safeboosc.eu, because they are in *equipoise* as it relates to the balance between potential benefits and harms of this type of monitoring.

Significant harm is unlikely. Skin marks due to heat and pressure are seen but are rarely serious. But, mismanagement due to falsely low readings, or due to faulty reasoning when trying to respond to cerebral hypoxia is possible.

In any case, adding another sensor, another cable, another screen, and another number to the already crowded neonatal intensive care environment that surrounds such small and frail, newborn patient, and the parents—is likely to disturb even more.

And we should not disturb—unless necessary.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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