Title:

Cerebral near-infrared spectroscopy guided neonatal intensive care management for the preterm infant.

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on behalf of the ESPR Special Interest Group 'Near InfraRed Spectroscopy' (NIRS)

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Category of study: Review

Impact:

Near-infrared spectroscopy (NIRS) provides cot-side, real-time information on blood and oxygen supply to the brain. Therefore, it is a valuable tool to better understand the pathophysiology underlaying disease processes.

Current evidence suggests that NIRS-guided treatment in extremely preterm infants during transitional circulation does not improve clinical outcomes.

Specific training is needed to maximize potential performance.

Pathophysiological interpretation of cerebral NIRS data in the given clinical context may help in decision-making.

Appropriate use of this monitoring technique, interpreted concurrently with other routine parameters, is a potential clinical tool to guide interventions in the NICU setting.

Abstract

Infants requiring admission to the neonatal intensive care unit (NICU) are particularly vulnerable to developing brain injury. The severity of the underlying clinical conditions and the complexity of care call for continuous, cot-side, non-invasive monitoring tools. Near-infrared spectroscopy (NIRS) measures the regional tissue oxygen saturation of hemoglobin ($rStO_2$) and provides continuous information on the net-result of several factors. Cerebral $rStO_2$ correlates with echocardiography-derived measures of blood flow. Cerebral fractional tissue oxygen extraction provides information on the balance between oxygen supply and demand and can be continuously derived from the combined use of cerebral $rStO_2$ and arterial oxygen saturation. Information on cerebral blood flow autoregulatory capacity can be obtained from combining cerebral $rStO_2$ and invasive blood pressure monitoring by appropriate software. Cerebral $rStO_2$ provides real-time, end-organ information on perfusion-oxygenation, and when interpreted in the clinical context based on pathophysiological principles may be used as a help to guide interventions in the NICU. In this review we will discuss how to optimize NIRS monitoring for application in the NICU, with a particular focus on the preterm infant.

Introduction

Infants requiring admission to the neonatal intensive care unit (NICU) constitute a population at high-risk of developing brain injury. The first hours after birth are often critical, particularly in the preterm infant. During transition to extrauterine life, there may be imbalances between blood flow and oxygen delivery to the brain due to disturbed or delayed hemodynamic adaptation[1]. Low and fluctuating cerebral blood flow patterns are associated with adverse outcomes[2-4]. The vulnerability of this population, the severity of underlying clinical conditions, and the complexity of care call for continuous, cot-side, and non-invasive monitoring tools. A more comprehensive assessment of the critically ill newborn incorporating end-organ monitoring with high time resolution to guide interventions represents a next logical step.

Spatially resolved near infrared spectroscopy (NIRS) measures the regional tissue oxygen saturation of hemoglobin ($rStO_2$). The relatively thin superficial tissues (skin, scalp and skull) in newborn infants permit to obtain a signal with a dominating 'brain component'. The derived $rStO_2$ is a percentage of tissue oxygen saturation, corresponding to mixed oxygen saturation values representing predominantly the larger venous compartment. Thus, in the clinical setting $rStO_2$ is used as a surrogate measure for venous oxygen saturation and oxygen extraction[5]. Cerebral $rStO_2$ correlates with echocardiography-derived measures of superior vena cava return[6], and used in combination with invasive blood pressure monitoring, can provide estimates of cerebral blood flow autoregulation capacity[7-9] . Furthermore, assessment of the complexity of cerebral NIRS-derived signals, i.e. the ability to react to

physiological changes resulting in more irregular patterns, may be relevant with high complexity reflecting health and low complexity being associated with physiologic stress and complications such as intraventricular hemorrhage (IVH)[10]. The balance between oxygen supply and demand can be estimated in real time using pulse oximetry (SpO_2) and NIRS calculating the cerebral fractional tissue oxygen extraction (FTOE) from the ratio (SpO_2-$rStO_2$)/SpO_2 [4]. Employing FTOE effectively compensates for variations in SpO_2, offering a more accurate representation of perfusion, under the assumption of a consistent metabolism and oxygen demand within the assessed tissue and at the cost of including the errors in measuring SpO_2.

Neurovascular coupling in preterm infants, explored through EEG and NIRS, elucidates the complex interplay between neural activity and cerebrovascular dynamics. Neurovascular coupling drives the increase in cerebral blood flow with increased cerebral activity to satisfy the metabolic demands [11-14]. Excitatory signals, such as synaptic activity and neurotransmitter release, induce this phenomenon, unveiling the mechanistic intricacies that govern cerebral hemodynamic responses[11].

NIRS, as a non-invasive, continuous monitoring system, helps to adjust interventions that have effects on blood and oxygen supply to the brain. Therefore, NIRS may provide useful, real-time information on cerebral oxygenation, especially when interpreted together with other physiologic parameters measured in the NICU. The purpose of this review is to discuss how to optimize NIRS monitoring and identify clinically relevant situations for application in the NICU, primarily in the high-risk preterm infant.

NIRS monitoring in NICU

Pathophysiological approach

From a pathophysiological viewpoint, cerebral hypoxia may be due to one, or more often several interrelated factors. Overventilation may cause decreased brain perfusion due to hypocapnia, lung over-expansion may cause impaired cardiovascular function or there may be insufficient oxygen transport due to hypoxaemia. Poor cardiac contractility may result in low cardiac output and decreased brain blood flow and low oxygen-carrying capacity occurs with anaemia. Interventions for each of these problems are readily available in routine clinical practice, but the selection of the optimal treatment requires understanding of the underlaying pathophysiology derived from clinical data and monitoring parameters (Fig.1). Routine physiological parameters, central-to-peripheral temperature difference, transcutaneous or exhaled carbon dioxide, sequential blood samples for blood gases, hemoglobin, lactate and electrolytes, combined with NIRS may allow a more comprehensive and meaningful overall clinical assessment. Additionally, imaging (X-ray, echocardiography, lung or cranial-Doppler ultrasound) may help to further diagnose specific conditions.

The combined use of cerebral NIRS continuous monitoring and a dedicated treatment guideline has shown to stabilize brain oxygenation in the extremely preterm infant during transitional circulation[15,16]. This pathophysiological approach lists options suggested to address episodes of cerebral saturation out of range, focusing on respiratory and circulatory support.[15] The guideline was developed to improve the utility of NIRS for neuromonitoring in the target

population, which may require slight modification when used in other patient groups. The options can be ordered as steps in a pre-established sequence or considered as a list to be checked against the infant's clinical condition depending on the physician's assessment and local clinical protocols.

Trend monitoring versus absolute values

NIRS does not require pulsatile flow so the device also works during low flow states and states with low pulse pressure. Cerebral oximetry detects alterations of oxygenation faster than pulse oximetry[17] mainly due to device-specific averaging times. However, the sensor re-application precision and the reproducibility of absolute levels of oxygenation across the various commercial devices are relatively poor[18-20]. In addition, absolute value thresholds may be also population-dependent and clinical conditions such as postnatal age, presence of shunts, threshold for anemia, or type of mechanical ventilation among others, contribute to the difficulties to define absolute numbers for cerebral hypoxia or hyperoxia.

An observational study conducted within the first 24 hours from birth in infants below 28 weeks of gestation, using the NIRO-200NX oximeter, found a cerebral oximetry threshold of 71% to differentiate between infants who developed IVH and those who did not.[21] The investigators also reported that the time spent in cerebral hypoxia was also longer in the former.

Two phase-II trials[16, 22] and two large, phase-III randomised trials[23,24] were based on the use of absolute thresholds. The COSGOD Trials [22, 24] used combined pulse oximetry and NIRS monitoring to reduce the burden of cerebral hypoxia (below the 10th percentile) and cerebral hyperoxia (above the 90th percentile) during immediate stabilization (first 15 minutes after birth) in preterm infants, taking as

the 10th percentile at 15 minutes of age for cerebral hypoxia the $rStO_2$ value of 66%. These reference values were obtained using the INVOS 5100 oximeter with the neonatal sensor in a cohort of term and preterm infants who had no need of medical support, born either by caesarean section or vaginal delivery[25]. The SafeBoosC Trials [16,23] aimed to test the utility of cerebral NIRS-guided management of the extremely preterm infant during the first 72h from birth. The thresholds for cerebral hypoxia and hyperoxia were established as measured by the INVOS small adult sensor, and set at 55% $rStO_2$ and 85% $rStO_2$, respectively, although the upper threshold was only applied in the phase-II trial[16]. The corresponding values according to a variety of oximeters and sensors were established in a blood-lipid phantom[20]. In both phase-II trials [16, 22] the burden of cerebral hypoxia was significantly reduced, whereas none of the two large randomised trials, SafeBoosC-III[23] or COSGOD Trial [24] provided good evidence of clinical benefit of NIRS-guided management when guided by absolute thresholds in the preterm infant population.

The choice of a suboptimal threshold could have resulted in reduced benefits from treatment. Also a better definition of the study population, of the interventions influencing $rStO_2$ according to disease state or timing, or the condition to address could possibly enable NIRS monitoring to improve relevant clinical outcomes.

Need for specific training

The added value of cerebral NIRS compared to other routine clinical devices thus remains a matter of debate. NIRS-related clinical decisions and their impact on the infant's condition were investigated in a post hoc analysis[26] of the intervention group ($rStO_2$ visible) of the SafeBoosC phase II randomized clinical trial[16]. Three

quarters of all alarms due to cerebral hypoxia or hyperoxia were not followed by an active intervention, indicating that the infant's status was considered clinically stable, or the deviation was considered likely to recover spontaneously. However, approximately one quarter of NIRS alarms triggered a clinical intervention derived from the treatment guideline resulting in a positive change in the infant's clinical condition ($rStO_2$ returning to the 'normal range'), supporting the strengths of NIRS monitoring[26]. Of note, statistically significant differences were found among the participating centres in relation to the intervention chosen. The authors postulated this could be due to differences in the infant condition but was more likely related to the involvement of the study investigators and the training on NIRS of the involved physicians and nurses who delivered the 24/7 clinical care of the infants who took part in the trial. This could also explain, at least in part, the fact that treatment guided by cerebral $rStO_2$ monitoring for the first 72 hours after birth was not associated with a lower incidence of death or severe brain injury at 36 weeks' postmenstrual age compared to usual care in the extremely preterm infant in the large, pragmatic phase-III trial[23]. Thus, in this trial, only 29% of participants in the experimental group had a note on change of management due to cerebral hypoxia in their clinical records.

Target groups for NIRS monitoring in the NICU

The potential candidates for continuous NIRS cerebral monitoring as a component of a neuroprotective strategy would include newborns during stabilization in the delivery room, extremely preterm infants during the first days of extrauterine transition, newborns with hemodynamic or respiratory instability, neonatal encephalopathy, or undergoing complex surgery. Apart from the first two indications, investigated by randomized clinical trials, this review is based on limited observational studies, warranting additional evidence to substantiate potential therapeutic benefits.

Neonatal stabilization

Clinical assessment of the preterm infant during fetal to neonatal transition in the delivery room is complicated by high interobserver variability[27]. Measuring SpO_2 and heart rate in the delivery room is currently the standard of care; however normal range SpO_2 does not indicate adequate oxygen delivery to the brain[28]. Reference ranges of cerebral $rStO_2$ and cerebral FTOE in neonates who did not require intervention immediately after birth have been reported[25], although they are device-specific[20]. Observational studies point towards increased risk of IVH[29,30] and death[30] in preterm infants with significant cerebral hypoxia within the first 15 minutes after birth.

A randomized clinical trial tested the feasibility of NIRS-guided respiratory and supplemental oxygen support during resuscitation, compared to standard management (NIRS non-visible) to reduce the burden of cerebral hypoxia and hyperoxia in preterm infants[22]. Despite similar SpO_2 values initially, both SpO_2 and heart rate increased earlier, and mean supplemental oxygen was lower by 5

minutes in the NIRS visible group when compared with standard care. The multinational randomized confirmatory clinical trial (COSGOD-III) demonstrated that targeting cerebral $rStO_2$ using a treatment guideline immediately after birth did not result in higher survival without cerebral injury in the preterm infant below 32 weeks[24]. The authors suggest a lack of current effective interventions to improve cerebral $rStO_2$ within the first 15 minutes after birth might have caused this negative finding. The authors conclude that further trials are warranted to explore whether subgroups of infants may have a substantial benefit and which cerebral NIRS guided interventions might improve cerebral oxygenation the most. The impact of umbilical cord management strategies on cerebral oxygenation in the first hours after birth can be impactful and needs further research[31, 32].

The extremely low gestational age neonate during extrauterine transition

The immature cardiovascular system frequently fails to adequately adapt after birth, leading to decreased cardiac output and abnormal blood flow distribution. Altered brain perfusion and insufficient oxygen delivery to the brain may be the consequence. Some studies have shown an association between cerebral $rStO_2$ levels during the first days of life and neurodevelopmental outcomes[33,34]. Alderliesten et al[33] found an association between low $rStO_2$ (<50% lasting >10% of the observation period, monitored by INVOS 4100-5100) and lower neurodevelopmental scores, assessed at the corrected age of 18 and 24 months. The authors used the Griffiths Mental Scale (GMS) (at 18 months), and either the GMS, the Bayley Scales of Infant Development Second Edition (BSID-II), or the Bayley Scales of Infant and Toddler Third Edition (BSITD-III) (at 24 months). This observation was true regardless the need for cardiovascular support due to

hypotension, according to protocol. Using the same oximeter and simultaneous SpO_2 monitoring, Verhagen et al[34] studied a cohort of infants below 32 weeks over a 2-hour period on days of life 1, 2, 3, 4, 5, 8 and 15. Infants were followed up until 2 to 3 years of age when neurodevelopmental status was assessed using the BSITD-III. The authors found an association between cerebral oxygenation during the first two weeks after birth and outcomes. The largest effect sizes were found on day 1, within the lower and highest quartiles of $rStO_2$ and poorer cognitive outcomes, and between the highest quartile of FTOE values and poorer total motor outcomes. In addition, poorer fine motor skills were associated with a higher percentage of time spent with $rStO_2$<50% on day of life 1.

The SafeBoosC-II trial demonstrated that cerebral oxygenation can be stabilized in the extremely preterm infant during the first 72 hours from birth using $rStO_2$ monitoring and a pathophysiological, brain-oriented treatment guideline[15,16]. The primary effect was a reduction in the burden of cerebral hypoxia. Early surrogate outcomes, such as amplitude-integrated electroencephalography (aEEG) at postnatal day 3, molecular biomarkers of brain injury or neuroimaging did not significantly differ between the study groups[35,36]. Post-hoc analysis, disregarding intervention groups, however, revealed that high burden of cerebral hypoxia was associated with low burst rate on aEEG, severe IVH, and death[37]. The association between the burden of cerebral hypoxia and the 2-year outcome was prospectively addressed in the cohort of infants enrolled in the SafeBoosC-II trial using the BSID-II or BSITD-III and/or the Ages and Stages Questionnaire. [38] In a post-hoc analysis, infants were classified as low burden of hypoxia (first three quartiles) or high burden of hypoxia (4^{th} quartile). The rates of cerebral palsy (OR 2.14 (0.33-13.78))

and severe neurodevelopmental impairment (OR 4.74(0.74-30.49)) were higher in the high hypoxia burden group although not statistically significant. The confidence intervals were wide, and a clinically relevant association could not be excluded in this underpowered study. The potential benefits and harms of cerebral NIRS and a dedicated treatment guideline in the management of extremely preterm infants during early transition was not confirmed in the SafeBoosC-III randomized clinical trial[23,39,40]. Better indication of patients' subgroup for intervention are probably the next step.

Circulatory failure

Diagnosis of low blood flow states

Blood flow, oxygen transport and cellular metabolism are interdependent and complex phenomena. The perfusion pressure depends on cardiac output and systemic vascular resistance. At micro-circulation level, peripheral blood flow is regulated by the smooth muscle tone in small arteries and arterioles, and changes in venous capacitance. Tissue blood flow is adjusted according to oxygen demand. When cerebral blood flow/oxygen demand is unbalanced, cerebral FTOE may be increased up to a 'threshold' level where hypoxia-ischemia occurs. In addition, ischemia-reperfusion injury is one of the main determinants in the pathophysiology of IVH in the preterm infant[4,41,42], describing the occurrence of cerebral hemorrhage following recovery of a previously low flow state[4, 42].

Clinical assessment of circulatory status should consider a combination of biomarkers to guide cardiovascular treatment[43] as described in Figure 1. Cerebral NIRS may be an important adjunct to assess the adequacy of circulation. Failure to deliver oxygenated blood to the organs (and brain) due to circulatory impairment

will most likely result in decreased cerebral $rStO_2$. A prospective observational study conducted in extremely preterm infants within the first 3 days after birth, using serial echocardiographic and cranial Doppler scans, and continuous NIRS monitoring, showed a distinct pattern of cerebral and systemic hemodynamics in infants who developed IVH and those who did not. Lower left ventricular output, stroke volume and $rStO_2$, and higher FTOE were observed during the first 12h in the former[42]. These parameters tended to be equal to that in patients without hemorrhage around 28 hours, when IVH was detected. In addition, other NIRS-derived parameters may also be helpful to interpret hemodynamics. For example, impaired cerebral blood flow autoregulation, assessed by NIRS, has been shown to be a sensitive and specific measure to identify infants with low superior vena cava (SVC) flow and adverse outcome[7,8]. Severe hypotension (mean arterial blood pressure < gestational age -5 mmHg) is associated with impaired autoregulation (likely indicating the lower limit of the autoregulatory plateau), and predicts low SVC flow[7].

Guiding cardiovascular support

An example of how cerebral $rStO_2$ monitoring may help guide clinical decision-making during suspected low flow states is shown in Figure 2. If low cerebral $rStO_2$ is judged to be the consequence of impaired systemic circulation, either volume expansion, vasopressor-inotrope, inotrope, or a combination of interventions may be attempted[15,44-48]. Use of cardiovascular support has been associated with impaired autoregulation and cerebral pressure-passive circulation[7,8,45,49-51]. Of note, cerebral low $rStO_2$ may be the sole parameter indicating that systemic (and cerebral) blood flow is compromised in an infant who is otherwise well (Fig.2). In

this circumstance, increasing afterload by the use of vasopressors may be counterproductive to tissue blood flow and oxygenation[1], due to predominant α-adrenergic receptor stimulation causing further myocardial depression, protracted systemic hypoperfusion, and decreasing trends in cerebral $rStO_2$. Step-down titration of vasopressors may be more appropriate in these situations, under a pathophysiological approach, though evidence to support this policy is lacking. Conversely, stable cerebral oxygenation, even in rather low blood pressure ranges, might indicate adequate perfusion and preserved autoregulation, supporting a non-intervention approach[7,52].

Management of patent ductus arteriosus (PDA)

PDA is the most common cardiovascular condition in the preterm infant. A PDA with a high left-to-right transductal shunt volume potentially leads to decreased systemic blood flow and oxygen supply. Scoring systems to evaluate the magnitude and clinical relevance of transductal left-to-right shunting are available[53,54].

Cerebral NIRS monitoring could help in decision-making, alerting clinicians to the need for echocardiographic assessment to rule out a significant PDA. Cerebral $rStO_2$ is inversely related to ductal diameter[55] and N-terminal pro-brain natriuretic peptide[56]. Reported values of cerebral $rStO_2$ in infants with a hemodynamically significant PDA are between 10% to 14% lower than their matched controls[57]; sustained increases in blood pressure and cerebral $rStO_2$, and decreased FTOE were found up to 12 hours after a successful course of indomethacin. The effect of a hemodynamically significant PDA on cerebral $rStO_2$ was not confirmed in another study[58]. The direct effect of the medication used to close the PDA on the cerebral

circulation is also probably related to the way it is administered, and can also be monitored by NIRS[57,59,60].

The adverse outcomes in infants who undergo surgical PDA closure is likely to be confounded by indication. Surgical closure, however, carries a risk of significant hemodynamic changes. Post-ligation cardiac syndrome may complicate the postoperative course, particularly in the most immature infants[61]. Longer-term follow-up of infants who fulfilled the criteria of post-ligation cardiac syndrome indicates a tendency toward higher risk of neurodevelopmental impairment[62].

In this context, it is of relevance that an observational study using intraoperative NIRS showed a short-lasting (2-5 min) increase in cerebral blood volume immediately after surgical closure of PDA but no change in $rStO_2$[63]. The oximeter used was the NIRO 300, that provides continuous information about changes in total hemoglobin concentration and its components (oxyhemoglobin and deoxyhemoglobin) in the interrogated tissue; from these parameters, changes in cerebral blood volume can be calculated in absolute terms[5]. The abrupt cessation of the ductal steal and the subsequent increase in blood flow to the brain should increase cerebral $rStO_2$. Therefore, an alternative explanation could be a sudden and short-lasting increase in systemic vascular resistance as PDA is ligated causing decreased myocardial contractility and venous return, which in turn would entail reduced preload and increased cerebral blood volume but not cerebral blood flow. Also, the mechanical effects of the thoracotomy itself may affect cerebral hemodynamics assessed by NIRS[64]. Lemmers et al[65] found no substantial changes in cerebral oxygen supply or extraction in infants undergoing surgical PDA closure during the procedure. Presurgical $rStO_2$ was lower and FTOE higher in this cohort,

compared with pretreatment period in infants successfully treated pharmacologically, indicating different pre-treatment clinical status or differences in hemodynamic significance (i.e. transductal left-to-right shunt volume). After clipping the ductus, cerebral $rStO_2$ showed a sustained recovery and values 24h from surgery were significantly higher than pre-clipping and like those reported for preterm infants without PDA. Therefore, NIRS parameters of cerebral oxygenation may offer additional valuable information around ductal management. To our knowledge, the effect of PDA device closure on cerebral hemodynamics have not been published to date.

Respiratory insufficiency

Influence of mechanical ventilation

The interaction between respiratory support and circulation is of utmost importance. Studies exploring the effect of changing intrathoracic pressures or ventilation patterns on hemodynamics have yielded different results, probably because of a variety of underlying lung pathologies, baseline cardiovascular status, or both[66-69].

Several studies focus on the hemodynamic effects of nasal continuous airway pressure (nCPAP) ventilation[68-72], some of them with direct assessment of cerebral oxygenation[70,71]. Using nCPAP at pressures up to 8 cm H_2O in a variety of lung conditions in preterm infants, even if a negative effect on right ventricular output and venous drainage is documented[72], did not appear to influence either routine monitoring of physiological parameters (heart rate and blood pressure) or on systemic blood flow (left ventricular output).

Effective sustained lung inflations followed by nCPAP during neonatal stabilization prevent cerebral blood volume decrease immediately after birth[73,74], but favor a raise in heart rate and cerebral $rStO_2$, followed by a rapid increase in SpO_2[75]. However, these perceived benefits may be of limited importance given the suspicion of negative effects on clinical outcome[76] .

The optimal pressure to prevent alveolar collapse without adverse hemodynamic effects depends greatly on lung compliance. Slight changes with either invasive or non-invasive mechanical ventilation, can potentially cause changes in cerebral oxygenation. As compliance improves, there is a potential risk of increased intrathoracic pressure affecting venous return to the right heart, and alveolar overdistension may compress the perialveolar capillaries causing increased pulmonary vascular resistance and decreased pulmonary venous return and cardiac output. Of note, in infants with very poorly compliant lungs, insufficient lung recruitment could be the main determinant of hypoxia (low SpO_2). An X-ray or lung ultrasound may help to elucidate whether a moderate increase in mean airway pressure could help to improve the infant's condition. Usually, the positive effect of lung recruitment on SpO_2 and cerebral $rStO_2$ trends occurs in seconds-minutes. Therefore, individual pathophysiological assessment, including NIRS, could help to interpret the clinical context and guide interventions in a variety of settings (Fig. 3).

PCO_2 vasoreactivity

One of the most important determinants of cerebral blood flow and cerebral oxygen dynamics is partial pressure of carbon dioxide (PCO_2). During the acute phase of respiratory distress syndrome, infants on assisted ventilation, even if on

targeted ventilation, may have inadvertent low PCO_2 or a fast descent within the normal range. Fast changes in PCO_2 may have pronounced effects on blood flow to the brain due to the blood-brain barrier that restricts diffusion of HCO^- over the course of time, so that buffering is less effective [9, 77]. A positive correlation between PCO_2 and cerebral $rStO_2$, and a negative correlation between PCO_2 and FTOE has been described in mechanically ventilated preterm infants associated with spontaneous PCO_2 changes[78]. Acute end-tidal (et) CO_2 fluctuations (variations of 5 mmHg or more lasting less than 1 hour) in infants below 32 weeks of gestation affect brain oxygenation and electrical brain activity, even if PCO_2 levels remain within the physiological range [79]. During acute $etCO_2$ decreases, $rStO_2$ decreased and FTOE increased with recovery after $etCO_2$ returned to baseline; significant increase in spontaneous activity transients per minute was also found. Opposite changes occurred during acute $etCO_2$ increases.

NIRS trend monitoring could assist in blood gas monitoring in mechanically ventilated infants. Further studies should address the role of NIRS monitoring in the absence of transcutaneous or exhaled CO_2 monitoring as an early warning system, as inadvertent hyperventilation is associated with periventricular leukomalacia and cerebral palsy[80].

Other aspects of critical care in NICU

Oxygen transport capacity

NIRS may guide neonatologists to transfuse infants with low hematocrit. Blood oxygen-carrying capacity depends on the hemoglobin concentration. Stable preterm infants with low hematocrit may be in an unrecognized high cardiac output state[81,82]. Trends in NIRS monitoring (brain and peripheral organs) may

detect subclinical signs of oxygen delivery-demand imbalance that may not be detected by routine cot-side monitoring. An increase in cerebral $rStO_2$[83-87] and decreased FTOE[83,84,88,89] have been shown in a series of observational studies conducted in anemic preterm neonates with a variety of low hemoglobin thresholds following packed-red blood cell transfusion, and suggest an immediate benefit of transfusion, although this may not translate to decreased risk of death or moderate-severe neurodevelopmental impairment at follow up[89].

Routine care and handling

NIRS monitoring can also help to interpret the effects on cerebral oxygenation of routine care in sick infants, such as apnea and/or bradycardia episodes[90], endotracheal suctioning[91], positioning while on assisted ventilation[92], surfactant administration[93], assessment of extubation readiness[94], influence of oxygen saturation target range[95], intravenous glucose infusion[96], type of feeding[97], umbilical catheter manipulation[98,99], painful procedures[100,101], environmental factors such as noise[102], sleep cycles[103], or kangaroo care[104], amongst others.

Summary

In this state-of-the-art review, we discussed the rationale for the use of cerebral NIRS-targeted treatment in the NICU setting, with a focus on the preterm infant. The potential added value of cerebral $rStO_2$ and other NIRS-derived parameters is to help interpret the pathophysiology that underlies disease states and assess the effects of interventions. Although apparently an easy-to-use cot-side monitoring tool, the uptake of NIRS monitoring during a multicenter clinical trial differed significantly among centers[26], most likely related to specific training and learning curves. These facts, and maybe the selection of patients for intervention, could have had an influence in the lack of positive effect on survival free of brain injury at term-equivalent age of two recently published confirmatory trials on cerebral NIRS-guided intervention[23,24]. Ongoing studies seek to determine whether interventions based on NIRS-derived parameters improve long-term clinical outcomes in extremely preterm infants[105]. Further evidence is needed before the use of cerebral NIRS can be generally recommended for the care of very preterm infants in the NICU, where any device, even if “non-invasive”, must have a clear benefit.

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Authors contribution:

All members of the European Special Interest Group “Near InfraRed Spectroscopy” are listed in the appendix. All these members have substantially contributed to the conception and revision of the manuscript and approved the final version to be published.

Financial support: None.

Disclosure: No author’s financial ties or conflicts of interest declared

Figure legends

Figure 1.

Pathophysiological approach to cerebral perfusion-oxygenation. Representation of the main components influencing cerebral oxygen transport and delivery and routine monitoring tools (PCO_2, partial pressure of carbon dioxide; SpO_2, pulse oximetry; A/V, arterial/venous; ΔT^{o}, central-to-peripheral temperature gradient; CRT, capillary refill time; MABP, invasive/non-invasive mean arterial blood pressure; Echo-D, Doppler ultrasound (brain and echocardiography).

Figure 2.

Twenty-eight weeks' gestation infant, first 10h from birth, haemodynamically stable, on mechanical ventilation. Blood gas showed moderate hypocarbia (PCO_2 32 mmHg) and blood lactate below 3 mmol/L. Cerebral NIRS trends were consistently maintained close to the hypoxic threshold (63% for the specific device- INVOS neonatal sensor)(panel A).

Echocardiography depicted low superior vena cava (SVC) flow and low right ventricular output (VO), proportionally high left VO, and a large patent ductus arteriosus (PDA) with reversed abdominal aortic flow (panel B). Dobutamine was started to overcome the haemodynamic workload imposed by PDA. The repercussions that were documented after 1 hour of effective dobutamine infusion were a small increase in heart rate, no change in blood pressure and a sustained increase in oxygenation, both at systemic and cerebral level (panel C).

Figure 3.

Recruitment maneuver in an infant with respiratory distress syndrome on high-frequency oscillatory ventilation and hypoxemia. Protracted hypoxia consistent on a negative effect of increased mean airway pressure (MAP) on cerebral oxygenation ($rStO_2$)(red circle) and the return to baseline after MAP is reduced.

Appendix

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