CEREBRAL NEAR-INFRARED SPECTROSCOPY IN TERM NEWBORNS: REFERENCE VALUES AND HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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Abstract

Non-invasive measurement of cerebral tissue oxygenation (cStO₂) using near-infrared spectroscopy (NIRS) is attracting an increasing attention not only in neonatology. The vast diversity of commercially available NIRS devices makes it difficult to compare in the published clinical studies. This review provides a view on the practical use of NIRS as a tool for cStO₂ measurement, its limitations and pitfalls, with a focus on brain dysfunction caused by hypoxic-ischemic encephalopathy. This syndrome of disturbed neurologic function in the earliest days after the birth in the term infants is manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness, and often seizures. This fascinating technology has already proven accurate and has been recommended to use during daily routine tool to evaluate the level of oxygen saturation in brain in intensive care units worldwide.

Key words: brain, hypoxic-ischemic encephalopathy, neonate, NIRS, oxygenation

INTRODUCTION

Non-invasive measurement of cerebral tissue oxygenation (cStO₂) using near-infrared spectroscopy (NIRS) is attracting an increasing attention in neonatology. This technology measures regional perfusion and oxygenation to provide a regional oxygen saturation level. As a bedside real-time technique it could help to identify under/over oxygenation levels in infants suffering from hypoxic-ischemic encephalopathy (1, 2). HIE is defined as a condition occurring in babies born over 35 weeks gestational age in which there is a disturbed neurological function (3). This syndrome of disturbed neurologic function in the earliest days after birth in the term infants is manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness, and often seizures (4, 5). The overall incidence of HIE is about one to two babies per thousand term livebirths (6, 7).

NEAR-INFRARED SPECTROSCOPY

NIRS has been introduced in clinical practice as a tool to measure regional perfusion and oxygenation to provide real-time tissue oxygenation. All NIRS devices emit light at wavelengths within 700 – 1,000 nm and analyse photons returning to the transducer (1, 8). However, the difference between the light emitted and the light measured is not only caused by absorption but also by scattering. If scattering is assumed to be equal for the different detectors, absolute values can be measured and oxyHb (oxyhemoglobin) and dHb (deoxyhemoglobin) can be calculated into ratio-based percentage oxygen saturation (oxyHb/(oxyHb+dHb); range 0 to 100%) using different algorithms and methods (Table 1) (9–12). Recent NIRS based devices obtain estimates of total cerebral oxygenation: TOI (Tissue

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Oxygenation Index) or StO_2 (regional oxygen saturation). This indifferent nomenclature is rather confusing; both indexes are used to calculate the fractional tissue oxygen extraction (FTOE), which represents the balance between oxygen supply and oxygen consumption. Modern devices incorporate the same technology but they differ in the number and absolute value of wavelengths, as well as in mathematic algorithms to translate the measured changes in light to absolute values (11, 12).

Table 1 Most used NIRS based devices for tissue oxygenation measurements (1–3, 11–13)

Type	Number of sensors	Manufacturer	Info
FORE-SIGHT®	2	Casmed, USA	www.casmed.com
FORE-SIGHT Elite®	4	Casmed, USA	www.casmed.com
INVOS™ 5100 C	2 – 4	Comanetics, USA	www.somanetics.com
NIMO™	4	NIROX, Italy	www.nirox.it
NIRO-200NX™	2	Hamamatsu, Japan	www.hamamatsu.com
02C™	2	LEA, Germany	www.lea.de
OxiplexTS™	2	ISS, USA	www.iss.com
TRS™	2	Hamamatsu, Japan	www.hamamatsu.com
EQUANOX 760™	4	Nonin, USA	www.nonin.com
ROOT®	2	Masimo, USA	www.masimo.com
T.oX™	2	ViOptix, USA	www.vioptix.com

A comparison of absolute values (cerebral, splanchnic, renal area) measured by different devices can be difficult (12). Name of the oxygenation saturation index may also vary: TOI (NIRO®, Hamamatsu Photonics, Japan), StO_2 (INVOS™ 5100 Somanetics/Covidien, Mansfield, USA or FORE-SIGHT®, Casmed USA) (1, 9).

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

HIE is a disorder in which clinical manifestation indicates a brain dysfunction. Most underlying pathologic events of HIE are complex, including impaired cerebral blood flow, oxygen delivery, and they evolve over time (13, 14). However, the pathophysiologic effects of the hypoxic-ischemic insult are complex and evolve over time. The unfolding of signs and symptoms makes it difficult for health care providers to determine timely appropriate treatment options. The pathologic events of HIE occur in two phases: primary energy failure and secondary energy failure (13, 14). The extent of primary energy failure contributes to further injury in the secondary energy failure phase. The exact mechanisms of secondary energy failure remain unclear but appear to be related to oxidative stress overproduction of free radicals, which cause damage to neuronal cell membranes and lead to necrosis or apoptosis, excitotoxicity, and inflammation (13, 14). The latent period (after primary energy failure phase but before secondary) is considered the optimal timing for therapeutic interventions (14). The current successful treatment for infants with HIE is therapeutic hypothermia. It has been documented that this method is effective because it reduces free radicals and glutamate levels, decreases oxygen demand, and decreases apoptosis (3, 4, 7).

REFERENCE VALUES FOR CEREBRAL OXYGENATION

A large amount of studies based on NIRS monitoring of neonatal brain has been published, during neonatal transition or later life period during this unique period of human life. The published values were influenced by the gestational age, mode of the delivery, and the type of NIRS device used (15). Urlesberger et al. demonstrated that mean cStO_2 during transition increased rapidly from 44% (3rd minutes) to 76% (7th minutes); thereafter no significant change occurred. They included 61 infants who were delivered via elective caesarean section. An INVOS 5100TM (Somanetics, Troy, Michigan) device and left frontoparietal area were used. Cerebral fractional tissue oxygen extraction (cFTOE) decreased during the first minutes of life, by which values of the brain did not change significantly after 5 minutes (16). Recently demonstrated reference ranges and percentile charts for cStO_2 , cFTOE using INVOS 5100TM (Somanetics, Troy, Michigan) in the large cohort of term/preterm neonates found no significant differences comparing term and preterm neonates (17). Average cStO_2 increased from 41.1 at 2nd minute to 79.4 at 10th minute and later slightly dropped to 77.5 in 15th minute (17). Although, cStO_2 of vaginally delivered neonates shows a decrease of up to 10% in value accompanied by the increase of FTOE after 8th minute of age (18-20). Both the immediate postnatal adaptation and the following phase were assessed with mean cStO_2 remaining between 70% and 80% during first 9 hours of life (NONIN EQUANOXTM 7600 Regional Oximetry System, USA) (21). Taken together, most of the published studies expect mean reference values of cStO_2 between 55% – 85% (in % values).

HIE AND CEREBRAL OXYGEN SATURATION VALUES

Therapeutic hypothermia soon after birth in the latent phase before the onset of secondary deterioration has been considered a feasible treatment in order to reduce the disabling neurodevelopmental sequelae of HIE (3, 6, 22). The study reported data from simultaneous aEEG (amplitude-integrated electroencephalography) and NIRS monitoring in newborns undergoing cooling following neonatal asphyxia suggested that TOI (NIRO[®], Hamamatsu Photonics, Japan) can be used as an early and reliable prognostic indicator of neurological outcome (6, 23). A higher TOI in infants with adverse outcome than with those with normal outcome has been documented ($80.0 \pm 10.5\%$ vs $66.9 \pm 7\%$, $p = 0.057$ at 6th hour of life, $79.7 \pm 9.4\%$ vs $67.1 \pm 7.9\%$, $p = 0.034$ in 12th hour of life). The authors concluded that the aEEG background pattern at 24 h of life loses its positive predictive value after therapeutic hypothermia initialization (6). Other study published by Peng et al. observed a significant changes in cStO_2 during the 72-hour duration of the hypothermia treatment, which led to important variations of oxygen demand/utilization. cStO_2 was higher in the asphyxiated newborns who developed later brain injury. Sensitivity within the first 10 hours of hypothermia treatment for the adverse outcome was 100% (95% CI, 70 – 100%) with a specificity of 83% (95% CI, 36 – 99%) (FORE-SIGHT[®], Casmed, USA). In all enrolled infants the authors noticed a decrease of cStO_2 from 1st hour to 4th hour of the hypothermia treatment. This time range seems to be the only time when temperature has a significant impact on cStO_2 and, thus, on the cFTOE (24). cFTOE remained stable in infants with normal outcome but decreased after 24 hours in infants with adverse outcome in different study (3, 25). Only a small number of studies showed combined use of aEEG and NIRS. Goeral et al. demonstrated this combination for outcome prediction in neonates cooled for HIE. For moderate HIE this double monitoring technique has proven as important predictors of short-term outcome. The highest predictive ability was documented between 18 hours and 60 hours of therapeutic hypothermia (the addition of NIRS to aEEG led to an increase in specificity (from 52.4–59.1% to 72.7–90.5%) (15, 26). The published data also showed a reduced predictive value of the evaluated scores after 60 hours and, therefore, their results might have been due to that unfavorable time point (26). However, in different study NIRS variables (INVOS 5100TM, Somanetics, Troy, Michigan) did not differentiate between those with favorable ($n = 13$) versus adverse (death or moderate-severe disability; $n = 5$) 18-month out-

comes. Systemic cStO₂ variability was higher during hours 48 – 72 of cooling among those with favorable outcomes: mean aEEG amplitude during hours 24 to 48 of cooling was higher among those with good outcomes (27).

CONCLUSION

This review summarizes an overview of current state of NIRS technology in the field of neonatology as a tool for non-invasive feasible method. The results of recently published studies have shown that monitoring of cerebral oxygenation can have an important role to play in the setting of treatment management of HIE. However, the differences between NIRS based devices (different wavelengths, different computing algorithm translating measured changes into the total value) complicates the comparison between them. It has been documented that values can also depend on the type of probe used (28). Since they should be single-used, routine NIRS monitoring can be costly. Some authors pointed out that reapplication of sensors on the same region can result in degree of inaccuracy of up to 6% (15, 29). More normative population-based data are needed in order to establish physiological values for different NIRS devices. Many different clinical conditions may complicate the NIRS values evaluation (hemoglobin concentration, blood pressure, persistent *Ductus arteriosus Botalli*, respiratory status, hyper/hypocapnia, and others) (1, 6, 11, 30). This should be mentioned and double checked, if possible, in every single study design. This field of neonatology has been extremely fascinating and evolving in recent years. As for screening tool for neurological outcome NIRS has already proven its simplicity and popularity as a power tool to be one step ahead in the treatment of our smallest and most vulnerable patients.

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