Cerebral oxygenation and autoregulation in preterm infants: Association with morbidity and mortality

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A. Problem Statement/ Rationale

Extremely preterm infants are at high risk for early hemodynamic instability. Poor modulation of vascular tone, variable responses to agitation, sepsis, development of a hemodynamically significant patent ductus arteriosus (hsPDA), and other factors may contribute to fluctuations in systemic blood pressure in the first few days of life. Moreover, preterm infants are at risk for altered cerebral autoregulation with increased periods of cerebral pressure passivity, potentially leading to the development of intraventricular hemorrhage (IVH) or white matter injury. It remains unclear whether disturbances in systemic blood pressure also result in compromised end organ perfusion. Near-infrared spectroscopy (NIRS) is a non-invasive technology, well suited to bedside monitoring of regional tissue oxygenation in these infants. *This protocol will investigate the utility of early NIRS measures in identifying preterm infants at highest risk for mortality and significant neonatal CNS morbidities including IVH and periventricular leukomalacia (PVL).* The novel approach of measuring regional tissue oxygenation as an indicator of end-organ perfusion may contribute substantially to the literature as well as to clinical practice. NIRS monitoring will provide the clinician with evidence of abnormal cerebral tissue oxygenation and impaired cerebral autoregulation. *We hypothesize that abnormal NIRS measures and increased cerebral pressure passivity in extremely preterm infants in the first 96 hours of life will be associated with mortality and the development of severe CNS morbidities.*

B. Specific Aims

1. Measure regional cerebral tissue oxygen saturations in the first 96 hours of life in extremely preterm infants and identify associations between NIRS measures and the following:
    a. Mortality prior to hospital discharge
    b. Severe CNS morbidity including IVH, ventriculomegaly, or PVL as diagnosed by cranial ultrasound in the first ten days of life.

2. Correlate the degree of cerebral pressure passivity in the first 96 hours of life as measured by simultaneous NIRS and arterial blood pressure monitoring with:
    a. Mortality prior to hospital discharge
    b. Development of severe CNS morbidity as defined above

C. Hypotheses

1. Lower cerebral tissue oxygenation levels and more frequent fluctuations in cerebral oxygenation will be associated with:
    a. Mortality
    b. Severe CNS morbidity

2. Increased periods of cerebral pressure passivity will be associated with:
    a. Mortality
    b. Severe CNS morbidity

D. Background/ Previous Studies

Brain Injury in prematurity

Modern perinatal care has improved survival rates for extremely preterm infants, but there has been little to no improvement in their neurodevelopmental outcomes. Preterm infants are at risk for fluctuations in blood pressure and oxygenation. Vulnerability and immaturity of the preterm brain may further predispose these infants to developing

intraventricular hemorrhage or ensuing white matter injury with long term neurological impairment. Hypotension itself may not lead to cerebral ischemia [1] and medications used to treat hypotension have different effects on cerebral blood flow [2]. Strategies to clarify the timing of insults to the brain and thus potentially intervene before injury occurs are essential. This study will focus on the detection of cerebral oxygenation abnormalities and impairment of cerebral autoregulation, which may identify which infants are at highest risk for ensuing brain injury.

NIRS principles

NIRS permits measurement of regional cerebral oxygenation. Unlike pulse oximetry, which is dependent on arterial pulsations, NIRS can effectively detect regional oxygenation during low perfusion states. It has most commonly been used to measure cerebral oxygenation, where near-infrared light is transmitted and detected by a sensor placed on an infant's forehead. Near-infrared light at different wavelengths is measured, and as oxy-hemoglobin (HbO_2) and deoxy-hemoglobin (HHb) have different absorption spectra, regional tissue oxygen saturation (rSO_2) can be calculated: $rSO_2 = HbO_2/(HbO_2 + HHb)$. This measurement is made at a depth of approximately 2.5-3 cm beneath the sensor. Assuming a weighted average of 20% arterial, 75% venous, and 5% capillary blood, the rSO_2 reflects a regional balance between oxygen supply and demand similar to a mixed venous oxygen saturation of the underlying tissue. While an absolute value of rSO_2 associated with tissue damage has not been standardized, an rSO_2 <40% during cardiac surgery may be associated with early post-operative neuropsychological dysfunction, a critical reduction in oxygen flux, EEG changes, and intracellular anaerobic metabolism and depletion of high-energy phosphates, especially when lasting longer than 10 minutes.[3-5] Hypoxia studies performed in piglets demonstrated neuronal mitochondrial injury in the hippocampal CA1 zone for cerebral rSO_2 values 30% to 40% and cellular vacuolization and fragmentation for rSO_2 <30%.[6]

NIRS is non-invasive, requires minimal caregiver attention once properly positioned, demonstrates good reproducibility in the neonate [7], and provides a continuous signal, which is not affected by changes in blood pressure, pulse, or temperature. However, interpretation of NIRS values must be made in the context of other factors that influence cerebral blood flow and oxygenation aside from anemia, such as mean arterial blood pressure, carbon dioxide tension, glucose levels, metabolic rate, and drug administration. NIRS monitoring has increasingly been utilized in a clinical neonatal intensive care setting for preterm infants including for evaluation of patent ductus arteriosus treatment, respiratory distress syndrome, therapy for hypotension, NEC, and anemia.

Impairment of cerebral autoregulation

Preterm infants are at higher risk for impaired cerebral autoregulation, which can also be readily detected using NIRS. NIRS measures of rSO_2 provide a good estimate of cerebral blood flow. [8-10] This approximation has been validated in animal studies using the gold standard radioactive microsphere technique [11, 12] and confirmed by transcranial Doppler ultrasound as a reliable method to assess for impaired cerebral autoregulation. [10] Specifically, concordance between mean arterial blood pressure and rSO_2 indicates a pressure passive cerebral circulation and presumed loss of autoregulation. [11, 13] The prevalence of pressure passivity has been quantified using a PPI defined as the percentage of 10-min epochs with significant coherence between mean arterial pressure (MAP) and rSO_2 signals in the low frequency range. [11] A NIRS study in preterm infants found that cerebral pressure passivity signifying loss of autoregulation occurred in a majority of premature infants with a mean PPI of 20%. [11]

Pressure passivity was associated with low gestational age and birth weight, systemic hypotension, and maternal hemodynamic factors. Loss of autoregulation with concordant changes between MAP and cerebral oxygenation in preterm infants was also significantly associated with increased severe IVH and PVL [12, 14] and with mortality [15] in single center studies.

Neurodevelopmental outcomes in preterm infants

Abnormal NIRS measures may be associated with poor outcomes in preterm infants. For example, decreased cerebral oxygenation and impaired cerebral autoregulation have been associated with the subsequent development of severe IVH or PVL [12, 16]. Clinical predictors currently associated with reductions in the risk of death or profound neurodevelopmental impairment include higher gestational age, exposure to antenatal steroids, female sex, singleton birth, and higher birth weight [17]. The addition of early NIRS measures to these clinical predictors may enhance a clinician's ability to counsel families regarding neurodevelopmental outcomes and the likelihood of intact survival in the preterm infant.

E. Methods:

1. Study Design

This multi-center, prospective observational pilot study will investigate NIRS monitoring of end organ oxygenation and cerebral autoregulation at six centers with previous NIRS experience with an estimated total enrollment of 100 infants over a one-year period. After enrollment, NIRS sensors will be applied to an infant's forehead to measure cerebral oxygenation within the first 96 hours of life. NIRS data, in addition to blood pressure and systemic oxygen saturation, will be continuously acquired until 96 hours of age or earlier if arterial access becomes unavailable. Data will be analyzed in 20-minute intervals to determine the mean cerebral oxygenation (rSO_2) and pressure passivity index (PPI as defined below), as well as a low rSO_2 index (time with rSO_2 <40%). Statistical analyses will include logistic regression and longitudinal modeling to determine the association between these NIRS measures and the development of in-hospital mortality or severe neurologic morbidities as previously described.

2. Study Population

Inclusion Criteria

Birth weight ≤1250 grams, indwelling arterial catheter, age < 24 hrs old

Exclusion Criteria

Lethal chromosomal abnormality, major congenital anomaly, decision not to provide full intensive care support, or skin integrity insufficient to allow placement of NIRS sensors

Enrollment of Subjects

Each participating center will be responsible for obtaining their own IRB approval and devising a screening strategy to identify potential subjects. Informed parental consent will be obtained prior to enrollment, either prenatally or postnatally.

3. Study Intervention/ Data Collection

After enrollment, a NIRS neonatal sensor (Covidien) will be placed on the infant's forehead for continuous monitoring of cerebral saturation. Clinicians will be blinded to rSO_2 measures by obscuring the monitor with a shield. NIRS sensors will be assessed on a daily basis to evaluate surrounding skin integrity and replaced as necessary. NIRS data in addition to continuous patient data including blood pressure and systemic oxygen

saturation will be acquired at a sampling rate of 1/30 Hz until 96 hours of life. Data will be collected using a Vital Sync bedside device allowing for data integration from the bedside monitor and INVOS. Blood pressure readings will be obtained from an indwelling arterial catheter. All data will be downloaded to media for secure electronic submission and subsequent processing by a central analyst. Data will be identified by study number only and will be maintained in a secure location. Total time with missing data will be ascertained. Of the remaining useful NIRS data, mean rSO_2 and PPI (total percentage time with concordance between rSO_2 and mean arterial blood pressure as determined in the very low frequency range (1/30 Hz)) will be calculated over 20 minute intervals. Concordance will be defined as a Pearson's correlation coefficient >0.5. Percentage of time with cerebral rSO_2 <40% will be defined as a low rSO_2 index. Blood gas pCO_2 levels will be collected for possible confounding effects of hypocarbia or hypercarbia on cerebral blood flow. Perinatal data including birth weight, gestational age, sex, time of blood transfusions, use of pressors, and Score for Neonatal Acute Physiology Perinatal Extension II (SNAPPE-II) will be utilized.

4. Statistical Considerations

Outcomes

The primary outcome measures will be mortality before hospital discharge and severe CNS morbidity. Severe CNS injury will be documented by evidence of grade 3 or 4 IVH, ventriculomegaly, or periventricular leukomalacia as suggested by echodensity on cranial ultrasound in the first ten days of life.

Sample Size Estimate

This study would be done at eight centers with an estimated total enrollment of 100 infants over a one-year period. Literature is unavailable regarding expected differences in NIRS measures for preterm infants with CNS morbidity or mortality. One hundred infants will yield 80% power at the 0.05 level of significance to detect an association between NIRS measures and morbidity-free survival if 8% of the variance in low rSO_2 index can be explained by the subsequent development of CNS-morbidity or mortality. Similar effect size can be expected for the predictor variable PPI. Power may be improved by the inclusion of covariates in the full logistic regression model.

Statistical Analysis

Analyses will include mixed effects regression models for repeated measures to examine the relationship between NIRS measures of low rSO_2 index, PPI, and the outcome of CNS-morbidity or in-hospital mortality. Analyses will be adjusted for gestational age, birth weight, sex, center, and SNAPPE-II. Secondary analyses may look at additional NIRS measures as predictors including fractional tissue oxygen extraction (FTOE) and degree of variability in cerebral saturation levels.

F. Risks/ Benefits

The risks of participation are minimal as the study uses non-invasive NIRS monitoring. The cerebral oximeter sensor is held in place by an adhesive backing. Skin irritation from the adhesive used to secure the sensors in place is a possible risk, but this has not been reported in the literature as a problem [8, 14, 15], and we have not seen it in our experience in very low birth weight infants [18]. Insufficient skin integrity to tolerate the sensors is an exclusion criterion for this study. Manufacturer recommendations are to change the sensor every 24 hours. However, our previous experiences with the NIRS sensors have allowed us to use one sensor for continuous data collection over 4 days

without difficulty, although frequent monitoring for skin irritation and effective adhesion of the sensors is required. Skin integrity will be monitored during the protocol and evaluated for breakdown by both the bedside nursing staff and the research coordinator. If the infant becomes clinically unstable due to manipulation of the NIRS device, the acquisition of data will cease and the NIRS sensor and monitoring will be discontinued. Any adverse events such as skin breakdown or increased sepsis rates among enrolled patients will be tracked and reviewed by the principal investigator.

While enrolled subjects may not directly benefit from participation in this study, the information gained may ultimately help to reduce or prevent brain injury in future preterm infants by improving understanding of the relationship of brain injury to changes in cerebral oxygenation and blood flow. The proposed study would also help to establish the utility of early continuous NIRS monitoring in the extremely preterm population. Results may serve as a basis for future strategies to prevent or ameliorate brain injury using NIRS as a monitoring device for both cerebral oxygenation and autoregulation.

H. References

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