Cerebral Oxygenation, Extraction, and Autoregulation in Very Preterm Infants Who Develop Peri-Intraventricular Hemorrhage

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Objective To test the hypothesis that near-infrared spectroscopy (NIRS)-determined patterns of regional cerebral oxygen saturation ($rScO_2$), cerebral fractional tissue oxygen extraction (cFTOE), and autoregulatory ability can identify neonates at risk for developing peri-intraventricular hemorrhage (PIVH).

Study design This case-control study is a subanalysis of 30 neonates who developed PIVH >12 hours after admission as part of a lager prospective observational cohort study comprising 650 preterm neonates born at ≤32 weeks' gestational age. PIVH was diagnosed by cranial ultrasound, performed at least once daily. Mean arterial blood pressure (MABP), NIRS-determined $rScO_2$, cFTOE, and MABP–$rScO_2$ correlation were monitored from birth to 72 hours of age.

Results Infants with PIVH received more inotropic drugs before being diagnosed with PIVH. Significantly more infants with severe PIVH needed treatment for patent ductus arteriosus. The MABP–$rScO_2$ correlation was >0.5 significantly more often before mild/moderate PIVH and after severe PIVH compared with controls. $rScO_2$ was higher and cFTOE lower in infants before severe PIVH.

Conclusion NIRS-monitored $rScO_2$ and cFTOE suggest cerebral hyperperfusion in infants with severe PIVH. Moreover, MABP–$rScO_2$ correlation indicates more blood pressure-passive brain perfusion in infants with PIVH. Continuous assessment of patterns of cerebral oxygenation and arterial blood pressure may identify those preterm infants at risk for severe PIVH and prompt consideration of preventive measures. *(J Pediatr 2013;162:698-704)*.

Peri-intraventricular hemorrhages (PIVHs) that become evident within the first hours of life in extremely preterm infants are mostly related to inflammatory factors and the intrapartum period.[1,2] In contrast, PIVHs diagnosed after 12 hours of life (late PIVH) are more often related to hemodynamic factors, including loss of cerebral autoregulation and a pattern of fluctuating cerebral perfusion.[3-6]

PIVH is an important factor in adverse neurodevelopmental outcomes, and numerous efforts to reduce its incidence have been made.[7] For example, prophylactic treatment of extremely preterm infants with indomethacin was found to decrease the incidence of severe PIVH.[8] Because late PIVH may afford a therapeutic window, early recognition of changes in cerebral hemodynamics and cerebral oxygenation before the appearance of PIVH may help decrease its occurrence.

Near-infrared spectroscopy (NIRS) can be used to assess regional cerebral oxygen saturation ($rScO_2$), cerebral fractional tissue oxygen extraction (cFTOE), and autoregulatory ability of the cerebral vascular bed.[9-11] NIRS is noninvasive and can be applied for extended periods without disturbing often-unstable patients.[10,12] We hypothesized that assessment of the pattern of cerebral oxygenation and autoregulatory ability of the cerebral vascular bed, as determined by NIRS, can identify infants at risk for developing late PIVH.

Methods

This study is a subanalysis of a prospective observational study of all infants admitted to the neonatal intensive care unit of Wilhelmina Children's Hospital with a gestational age of ≤32 completed weeks. The study was approved by the Medical Ethical Committee of the University Medical Center Utrecht. Parental informed consent was obtained for all infants.

Continuous data on $rScO_2$ and cFTOE captured by NIRS during the first 72 hours of life were collected prospectively.[10,13,14] These data were stored in an electronic database along with clinical, physiological, and cranial ultrasound (cUS) data. In this

cFTOE	Cerebral fractional tissue oxygen extraction
cUS	Cranial ultrasound
MABP	Mean arterial blood pressure
NIRS	Near-infrared spectroscopy
PDA	Patent ductus arteriosus
PIVH	Peri-intraventricular hemorrhage
ROC	Receiver operating characteristic
$rScO_2$	Regional cerebral oxygen saturation
SaO_2	Arterial oxygen saturation

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The authors declare no conflicts of interest.

Portions of this study were presented as a poster at the Pediatric Academic Societies' meeting, April 28-May 1, 2012, Boston, MA.

 http://dx.doi.org/10.1016/j.jpeds.2012.09.038

cohort of 650 infants, 146 infants developed PIVH. A total of 116 infants were excluded from analysis for reasons listed in Figure 1 (available at www.jpeds.com), leaving 30 infants with postnatal PIVH eligible for analysis. From among the 504 infants without PIVH, 60 infants were matched to the 30 infants with PIVH and served as the control group. Matching criteria were gestational age, birth weight, sex, and year of birth (ensuring equal treatment strategies).

Obstetric, intrapartum, and neonatal data were collected from the database and hospital records. In all infants, arterial oxygen saturation (SaO_2) was measured continuously by pulse oxymetry. Mean arterial blood pressure (MABP) was measured with an indwelling arterial catheter (in the umbilical, tibial, or radial artery) during the 72-hour study period. These variables were monitored simultaneously by NIRS-monitored $rScO_2$ and stored with a 1-Hz sample rate on a personal computer for offline analysis using Poly 5 (Inspector Research Systems, Amsterdam, The Netherlands). Arterial blood gas samples were obtained at regular intervals (at least every 4 hours). cUS was performed through the anterior fontanel as soon as possible after admission and repeated daily or more often as necessary.

PIVH was graded according to the classification scheme of Papile et al,[15] with grade I-II considered mild-moderate PIVH and grade III-IV considered severe PIVH. The presence or absence of a hemodynamically significant patent ductus arteriosus (PDA) was investigated at least daily based on clinical indices and confirmed by echocardiography (ie, left atrial and/or left ventricular dilatation, internal ductal diameter >1.4 mm/kg, left pulmonary artery end diastolic flow >0.2 m/s). Respiratory distress syndrome was graded as none, moderate (clinically as well as on radiography), or severe (requiring exogenous surfactant therapy). Blood pressure support before detection of PIVH on cUS was scored according to the scheme of Krediet et al[16] as 0, no support; 1, volume expansion and/or dopamine ≤5 μg/kg/min; 2, dopamine 5-10 μg/kg/min; 3, dopamine >10 μg/kg/min or dopamine + dobutamine ≤10 μg/kg/min; 4, dopamine + dobutamine >10 μg/kg/min; or 5, additional adrenaline and/or corticosteroids.

The NIRS-determined $rScO_2$ was used as an estimator for changes in regional cerebral oxygenation.[13] This variable provides absolute values, is less sensitive to movement artifacts, and allows comparisons over time.[10,17]

A 2-wavelength (730 and 810 nm) near-infrared spectrometer (INVOS 4100-5100; Somanetics, Troy, Michigan) was used. A transducer (small adult SomaSensor SAFB-SM; Somanetics) containing a light-emitting diode and 2 distant sensors (30 and 40 mm) was placed on the frontoparietal side of the infant's head and attached firmly with an elastic bandage to prevent displacement.[10] $rScO_2$ was calculated from the differential signals obtained from these 2 sensors, expressed as the venous-weighted percentage of oxygenated hemoglobin (oxygenated hemoglobin/total hemoglobin [oxygenated hemoglobin + deoxygenated hemoglobin]).[10,18] To investigate the balance between oxygen delivery and oxygen consumption, cFTOE was calculated as $(SaO_2-rScO_2)/SaO_2$. An increase reflects increased oxygen extraction by brain tissue, whereas a decrease suggests less utilization or increased delivery of oxygen.[19]

The correlation between MABP and $rScO_2$ was used as an estimator of cerebral autoregulation.[9,20] The validity of MABP–$rScO_2$ correlation as an estimate of cerebral autoregulatory ability has been established previously.[21] MABP–$rScO_2$ correlation coefficients were determined every minute over 10 average 1-minute periods. A MABP–$rScO_2$ correlation coefficient, r, >0.50 was considered to indicate a lack of cerebral autoregulation.[9,22]

For each infant, 2 periods were defined, one before detection of PIVH and one after detection. The period before PIVH covered the 24-36 hours (up to 36 hours when the interval between subsequent cUS examinations exceeded 24 hours) before the first detection of PIVH on cUS. The period after PIVH covered the 24 hours after detection of PIVH. The defined periods of controls were matched for postnatal age, to exclude physiologic evolution of the studied variables (ie, $rScO_2$ and MABP) from influencing the results. For evaluation of $rScO_2$, a mean $rScO_2$ value was calculated for both periods. The average cFTOE and the percentage of time with an MABP–$rScO_2$ correlation >0.5, average heart rate, and average SaO_2 level were also calculated for both periods. Artifacts in SaO_2, MABP, heart rate, and $rScO_2$ (caused by, eg, movement, blood sampling) were removed manually before results were calculated. For MABP–$rScO_2$ correlations, time periods with an SaO_2 <85% were not included in the analysis. All calculations were performed using in-house–developed software (SignalBase; University Medical Center Utrecht, Utrecht, The Netherlands).

Statistical Analyses

Clinical data are summarized as mean ± SD, median and range, or percentage as appropriate. Results are presented for the PIVH group as a whole and separately for the mild-moderate (grade I-II) and severe (grade III-IV) PIVH subgroups. The Student t test, Mann-Whitney U test, and $\chi 2$ test were used as appropriate. Patterns of pCO_2 were analyzed using a mixed-model approach for repeated measures, taking into account the individual patient (random intercept), allowing for a random slope over time and including group (case or control) as a factor. Data were analyzed using R 2.15.0 for Windows (R Foundation for Statistical Computing, Vienna, Austria). Receiver operating characteristic (ROC) curve analysis and optimal cutoff calculation were performed using MedCalc 12.3.0.0 (MedCalc Software, Mariakerke, Belgium). A P value <.05 was considered to indicate statistical significance.

Results

The clinical characteristics of the mild-moderate and severe PIVH groups are summarized in Table I. Analyzing all PIVH cases together showed that only the inotropics score was significantly higher in cases than controls (median, 3 [range, 0-5] vs 0 [0-5]; $P < .001$). For the 30 cases, the mean interval between the most recent cUS examination without PIVH and the first cUS examination with PIVH was 21 hours (range, 3-36 hours).