The Neu-Prem Trial: Neuromonitoring of Brains of Infants Born Preterm During Resuscitation—A Prospective Observational Cohort Study

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Objective To determine whether monitoring cerebral oxygen tissue saturation (StO_2) with near-infrared spectroscopy (NIRS) and brain activity with amplitude-integrated electroencephalography (aEEG) can predict infants at risk for intraventricular hemorrhage (IVH) and death in the first 72 hours of life.

Study design A NIRS sensor and electroencephalography leads were placed on 127 newborns <32 weeks of gestational age at birth. Ten minutes of continuous NIRS and aEEG along with heart rate, peripheral arterial oxygen saturation, fraction of inspired oxygen, and mean airway pressure measurements were obtained in the delivery room. Once the infant was transferred to the neonatal intensive care unit, NIRS, aEEG, and vital signs were recorded until 72 hours of life. An ultrasound scan of the head was performed within the first 12 hours of life and again at 72 hours of life.

Results Thirteen of the infants developed any IVH or died; of these, 4 developed severe IVH (grade 3-4) within 72 hours. There were no differences in either cerebral StO_2 or aEEG in the infants with low-grade IVH. Infants who developed severe IVH or death had significantly lower cerebral StO_2 from 8 to 10 minutes of life.

Conclusions aEEG was not predictive of IVH or death in the delivery room or in the neonatal intensive care unit. It may be possible to use NIRS in the delivery room to predict severe IVH and early death.

Trial Registration ClinicalTrials.gov: NCT02605733. *(J Pediatr 2018;■■:■■-■■).*

Infants born preterm who require extensive resuscitation at birth have a greater rate of intraventricular hemorrhage (IVH) and death.[1] Current methods of monitoring an infant born premature at birth include heart rate (HR) and peripheral arterial oxygen saturation (SpO_2). Neither allows direct assessment of the brain at birth. Noninvasive neural monitoring by near-infrared spectroscopy (NIRS) and amplitude-integrated electroencephalography (aEEG) has been shown to detect differences in early brain injury.[2-4] NIRS may allow for the detection of low regional blood flow earlier than blood pressure, lactate, or urine output.

Monitoring in the neonatal intensive care unit (NICU) may include neuromonitoring with aEEG and/or cerebral oxygenation with NIRS. However, monitoring in the delivery room remains minimal. Cerebral oxygenation and aEEG monitoring at birth may predict infants at risk for poor outcomes.

A few trials have attempted to bring aEEG and NIRS into the delivery room, but only for the monitoring of infants born near-term and at term, many of whom did not require resuscitation.[5,6] Delivery room monitoring of infants born preterm during resuscitation may lead to an improved understanding of how the brain of an infant born premature responds during this critical time, provide a physiological basis for changes in the resuscitation process, demonstrate the feasibility of such monitoring, be used to determine optimal practice for these vulnerable infants, and possibly improve their quality of life. These very early, potentially corrective changes in physiology may be able to protect the brain from permanent injury. The aim of this study was to provide preliminary data about brain activity and oxygenation during the birth transition and resuscitation.

Given the known relationship between extensive resuscitation and poor outcomes, such as IVH and death, we hypothesized that infants who died or had IVH would have lower brain oxygenation and electrical activity, as measured by NIRS and aEEG

aEEG	Amplitude-integrated electroencephalography
AUC	Area under the receiver operating characteristic curve
EEG	Electroencephalography
HR	Heart rate
IVH	Intraventricular hemorrhage
NICU	Neonatal intensive care unit
NIRS	Near-infrared spectroscopy
RMS	Root mean square
ROC	Receiver operating characteristic
SpO_2	Peripheral arterial oxygen saturation
StO_2	Cerebral oxygen tissue saturation

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after birth and during the first 72 hours of life. Our secondary hypothesis was that continuous monitoring of physiological cerebral changes of the newborn, beginning at birth, would help us predict IVH and death.

Methods

This was a prospective, observational cohort study conducted at a large community hospital, Sharp Mary Birch Hospital for Women & Newborns, between October 2015 and December 2016, and approved by the institutional review board, including the use of deferred consent. When possible, pregnant women who were dated at <32 weeks of gestation by their earliest ultrasound scan or last menstrual period were approached for consent. Antenatal consent was not always practical because some infants were delivered rapidly, providing little time between admission and delivery. Excluding these infants from the trial could potentially omit the sickest newborns.[7] As with our previous trials that used deferred consent, parents who did not supply consent before delivery were approached immediately after birth by the research team to provide written consent to enroll their newborn for further data collection. If a parent did not want his or her child to participate in the study, data collection was discontinued and previous recordings were destroyed. Study exclusion criteria included congenital anomalies and moderate-to-severe head bruising at birth.

We combined the ability to monitor brain cerebral oxygenation with NIRS and brain activity using a simplified 3-lead electroencephalography (EEG) setup (**Figure 1**; available at www.jpeds.com). NIRS was measured via a FORE-SIGHT Elite Absolute Tissue Oximeter (CASMED, Branford, Connecticut). The simplified method of EEG acquisition was used for 2 reasons, the first being the limited amount of surface area available for electrode placement on the scalp of the infant born preterm and the second being the need to rapidly acquire EEG signal after birth so that the maximum amount of the birth transition can be recorded.

We developed a system that would permit rapid placement of EEG and NIRS without delaying resuscitation. Both EEG and NIRS were acquired by the use of widely available, adhesive sensors approved by the Food and Drug Administration. We prepared the NIRS sensor forehead wrap to contain the 3 EEG leads (hydrogel) and the NIRS sensor. The 3 EEG sensors were positioned with 2 on the forehead (the active and ground electrodes) and 1 on the cheek (the reference electrode), and the NIRS sensor was located on the infant's forehead (**Figure 1**). The NIRS and EEG sensors were placed immediately after birth.

Given that the brain rhythms of the infant born preterm can be difficult to discern from various artifacts, we verified that our method of EEG acquisition detects true cerebral activity by using our setup to detect a predictable and stereotyped pattern of brain activity. During wakefulness, the healthy adult brain emits just such a pattern in the form of the "posterior dominant rhythm," which is very rhythmic in appearance and is easily seen. Our board-certified pediatric neurologist ran this setup on a healthy adult and confirmed that it reliably detects cerebral activity.

We filtered the EEG signal using a band-pass filter that eliminated frequencies <0.5 Hz and >32 Hz. These values were selected specifically to minimize low-frequency movement artifact and high-frequency muscle artifact while allowing the range of frequencies in which neonatal brain activity is observed to pass through. We calculated root mean square (RMS) amplitude from the EEG signal given by the following equation:

$$RMS = \sqrt{\frac{1}{N}\sum_{i=1}^{N} x^2\,(i)}$$

where x = input EEG amplitude in microvolts, N is the duration of the EEG signal, and i is the current. RMS amplitude provides an approximate estimate of the cerebral function monitor output that is commonly used in the NICU.[8] In this study, the RMS amplitude reflects the cerebral voltage (amplitude) at the active electrode over a given unit of time (we estimated the RMS amplitude from the EEG signal once every 2 seconds for the 10-minute delivery room recording window and every 1 hour in the case of the 72-hour NICU recording window). In addition, the RMS amplitude estimate is shown to be useful in neonatal EEG classification problems.[9-11] The EEG was evaluated by the pediatric neurologist and analyzed by a postdoctoral electrical engineer with specific expertise in processing neonatal EEG activity.

Measurements of cerebral oxygen tissue saturation (StO_2), SpO_2, and HR by pulse oximetry, mean airway pressure, and fraction of inspired oxygen concentration were recorded every 2 seconds in the delivery room and EEG (single-channel) continuously. They were captured with a purpose-built digital data acquisition system, MP150 (Biopac, Goleta, California). In the NICU, EEG and cerebral StO_2 were collected with the MP150 and HR by electrocardiogram. Mean arterial pressure and SpO_2 were captured from the bedside monitor (CARESCAPE; GE Healthcare, Milwaukee, Wisconsin) for 72 hours. Ultrasound scans of the head were performed within the first 12 hours and at 72 ± 6 hours of life and analyzed for IVH via the Papile grading system.

Statistical Analyses

Given the lack of published data on NIRS and EEG in infants who need resuscitation and develop IVH, we chose a convenience sample. Data were analyzed with SPSS (version 23; IBM Inc, Armonk, New York). Data were first verified for accurate data entry, formats, coding, and missing observations. The largest and smallest values for each variable were reviewed for accuracy and plausibility. Each variable also was examined for variability and frequency distribution, skewness, and kurtosis. Data subsequently were evaluated by using descriptive, univariate, and adjusted analyses. Multivariable analyses were conducted related to specific study aims. All significance tests were 2-sided with a critical alpha level of .05. Comparison of demographic and subject characteristics were made with logistic regression, χ^2, or Fisher exact testing for dichotomous and categorical variables, Student t tests for comparison of

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means at each 1-minute interval for continuous variables, and the Mann–Whitney *U* Wilcoxon rank-sum test was used as a nonparametric test for ordered categorical variables or for continuous variables failing to meet normal distribution assumptions.

Univariate and adjusted analyses between the dependent variable and each independent variable were performed to examine the crude associations between variables by using χ^2 or Fisher exact testing, ANOVA, Mann–Whitney *U* Wilcoxon rank-sum test, linear regression, or logistic regression. Repeated-measures analyses were performed via generalized estimation equation modeling.

Receivers operating characteristic (ROC) curves were generated to evaluate using the mean NIRS values for each minute in the first 10 minutes of life to predict the outcome of severe IVH and death and obtain the sensitivity, specificity, and predictive values. The optimal area under the receiver operating characteristic curve (AUC) was used to evaluate the differences in the curves.

Results

There were 127 infants <32 weeks of gestational age enrolled (**Figure 2**; available at www.jpeds.com), of whom 13 developed any-grade IVH and/or died within 72 hours (**Table I**). Severe IVH (grade 3-4) and/or death occurred in 4 infants in the first 72 hours. There were no differences in either cerebral oxygenation by NIRS or RMS voltage by EEG in the delivery room for the infants who developed low-grade IVH (**Figure 3**). Infants who developed severe IVH or death had lower cerebral StO_2 from 8 to 10 minutes of life (**Figure 4**; available at www.jpeds.com). An ROC curve demonstrated a cerebral StO_2 threshold of 66 at 7-10 minutes of life and had a sensitivity and specificity of 89% and 81%, respectively (**Figure 5**; available at www.jpeds.com) (AUC = 0.885, $P < .001$, 95% CI 0.775-0.996). The ROC curve for SpO_2 had a lower AUC for the first 10 minutes (AUC = 0.763, $P = .001$, 95% CI 0.630-0.897). In a final generalized estimating equation to control for repeated measures, chorioamnionitis and gestational age, NIRS was significantly associated with severe IVH or death ($P = .002$) (**Table II**). There were no major differences in the resuscitation interventions in the 4 infants who developed severe IVH/death (**Table III**) other than a greater average peak inspiratory pressure ($P = .01$).

Hemodynamic variables and EEG over the first 72 hours did not show significant differences other than cerebral StO_2 and blood pressure. There were lower cerebral StO_2 and mean arterial blood pressure in the first 12 hours of life for subjects with severe IVH and/or death (**Figure 6**; available at www.jpeds.com).

Table I. Demographics

Demographics	Neither IVH or death (n = 114)	IVH or death (n = 13)	*P* value
Gestational age, wk, mean ± SD	28 ± 2	26 ± 2	< .001*
Birth weight, g, mean ± SD	1204 ± 428	940 ± 301	.033*
Male, n (%)	55 (48)	9 (69)	.241
Cesarean delivery, n (%)	98 (86)	6 (46)	< .01*
Antenatal steroids, n (%)	109 (96)	12 (92)	.484
Chorioamnionitis, n (%)	37 (32)	11 (85)	< .01*
Magnesium sulfate, n (%)	104 (91)	10 (77)	.131
1-min Apgar, median [IQR]	6 [4,7]	4 [2,6]	.04*
5-min Apgar, median [IQR]	8 [7,8]	8 [5,8]	.12

*Significant $P < .05$.

Table II. Generalized estimating equation: the association of cerebral StO_2, GA, and chorioamnionitis with severe IVH and/or death

Clinical outcome	Beta	SE	*P* value	OR	95% CI
Cerebral StO_2	−0.106	0.034	.002	0.899	0.841-0.962
GA	−0.477	0.183	.009	0.620	0.434-0.887
Chorioamnionitis	−1.001	0.884	.257	0.367	0.065-2.078

GA, gestational age.

Discussion

This single-center, prospective study demonstrates a relationship between low cerebral hypoxia in the delivery room and adverse outcomes in infants born premature. Cerebral StO_2 in the first 10 minutes of life was able to predict which infants developed severe IVH and death. Low cerebral StO_2 was a stronger predictor than other antenatal factors except for gestational age for severe IVH/death.

There were not significant differences in the resuscitation between the infants who developed severe IVH/death or those who did not. However, the peak inspiratory pressure suggests that more aggressive ventilation may have been required during resuscitation in these infants. No studies have reported greater peak inspiratory pressures with severe IVH/death, but increased peak inspiratory pressure could impede central venous return and increase intracranial pressure, which may in turn affect cerebral oxygenation and the development of IVH. However, given the small sample (n = 4) size, it

Table III. Delivery room interventions

Interventions	Severe IVH and/or death (n = 4)	Low-grade IVH and no IVH (n = 123)	*P* value
No support	0	2	1.0
Supplemental oxygen	4	123	.12
CPAP	3 (75%)	101 (82.11%)	.56
Received PPV	4 (100%)	89 (72.4%)	.57
Maximum inspiratory pressure	29 ± 5	24 ± 3	.01*
Maximum FiO_2	70 ± 47	64 ± 28	.65
Intubation	4 (100%)	50 (40.65%)	.31
Surfactant given in delivery room	2 (50%)	44 (35.78%)	.62
Compression/epinephrine	0	0	.54

CPAP, continuous positive airway pressure; *FiO_2*, fraction of inspired oxygen; *PPV*, positive pressure ventilation.
Values are n (%) or mean ± SD.
*Significant $P < .05$.

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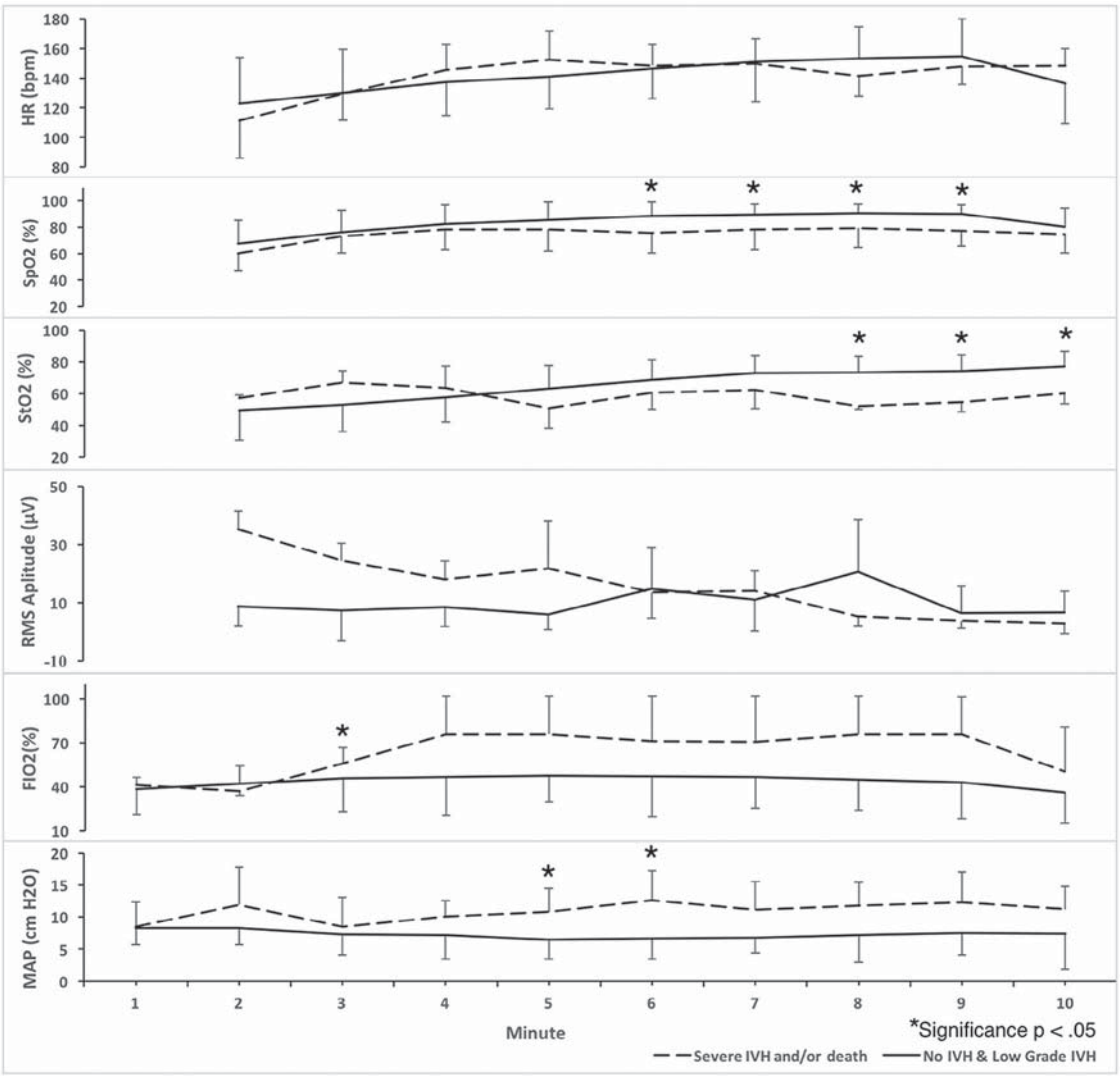

Figure 3. Delivery room measurements in the first 10 minutes of life for HR, SpO_2, cerebral StO_2, single-channel electroencephalogram (RMS amplitude), fraction of inspired oxygen (FiO_2), and mean airway pressure (MAP). The cerebral StO_2 at 8-10 minutes of life was significantly lower for subjects with severe IVH and/or death compared with subjects without the adverse outcome. *Significance $P < .05$.

is difficult to make any definitive conclusions, and our results may have been due to chance alone. This also may explain why no significant difference in EEG activity was seen.

Low cerebral StO_2 within the first few days of life is associated with adverse neurologic outcome and IVH.[11,12] In a single, small, observational study of 51 infants with very low birth weight, the 2 infants who developed IVH had cerebral StO_2 in the delivery room that was <10th percentile of the normative range.[13] A recent case-controlled study of 12 infants who had NIRS data at birth and developed IVH were matched with 12 infants with no IVH. The infants with IVH also had lower cerebral StO_2 during the first 15 minutes of life.[3]

Studies of EEG in the NICU have suggested that dampened electrical activity in the brain of the infant born preterm is associated with lower brain volume.[14,15] A single study of 47 infants in which the authors used NIRS and EEG, with only 16 infants from the cohort requiring some respiratory support, demonstrated a positive correlation between cerebral StO_2 and aEEG in the delivery room.[16] Our trial expanded and refined these results by demonstrating these findings in a larger and more immature cohort. We were also able to generate ROC curves that will aid future clinicians in the prediction of poor outcomes.

There are limitations to our trial. The cohort had a low number of infants with severe IVH and/or death. This limitation may have caused us to miss more significant differences in the delivery room and/or NICU with respect to clinical outcomes and other hemodynamic variables. Also, the poor performance of EEG using the RMS amplitude estimate suggests that cerebral function monitoring may not be a useful

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tool for predicting/detecting IVH due to artifacts caused by resuscitation and/or handling. With the help of advanced machine-learning techniques, it should be possible to analyze and interpret these EEG by eliminating artifacts.[17] Pichler et al demonstrated that amplitudes were different in more mature infants born at near term who required resuscitation compared with those who did not.[16] The authors used cup and gel electrodes, scrubbing the head before placement. Using this method, they could not obtain EEG results in most subjects prior to 3 minutes after delivery, so our study required a more rapid application setup to capture more of the birth transition. We used hydrogel-based electrodes and quickly wiped the foreheads of the infants before placement. Although the former method may be more effective, it would have been challenging in our immature population who required resuscitation. It is also possible our choice of electrode placement (frontal) over the traditional aEEG locations (parietal or central) may have not been able to detect precursors of IVH.

Resuscitation creates movement that introduces artifacts in the EEG signal, which may limit its usefulness in the sickest infants. Spontaneous movement from healthier infants can alter the appearance of the EEG signal as well. In contrast, NIRS is not affected by movement and maintains a stable reading during resuscitation.

aEEG performed in the delivery room or the NICU was not predictive of any morbidity. Cerebral oxygenation had a stronger association with severe IVH/death than chorioamnionitis or gestational age. Future studies may be able to increase the robustness to verify our findings. ■

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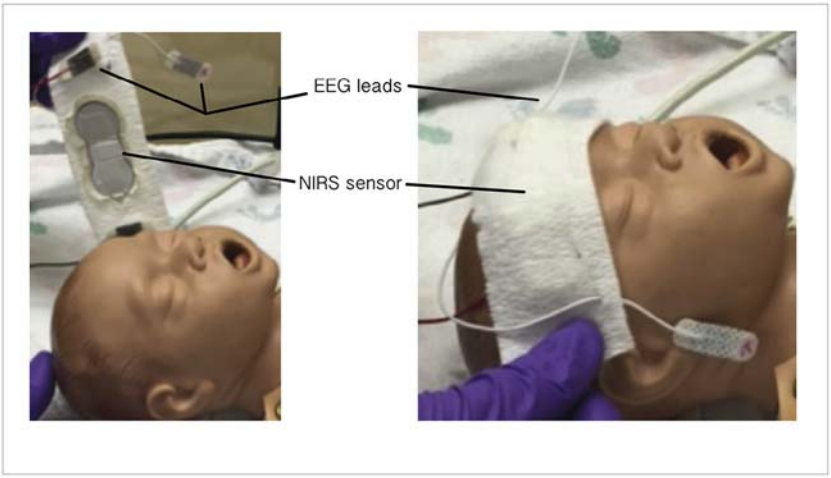

Figure 1. Forehead wrap with EEG leads and NIRS sensor for cerebral StO_2.

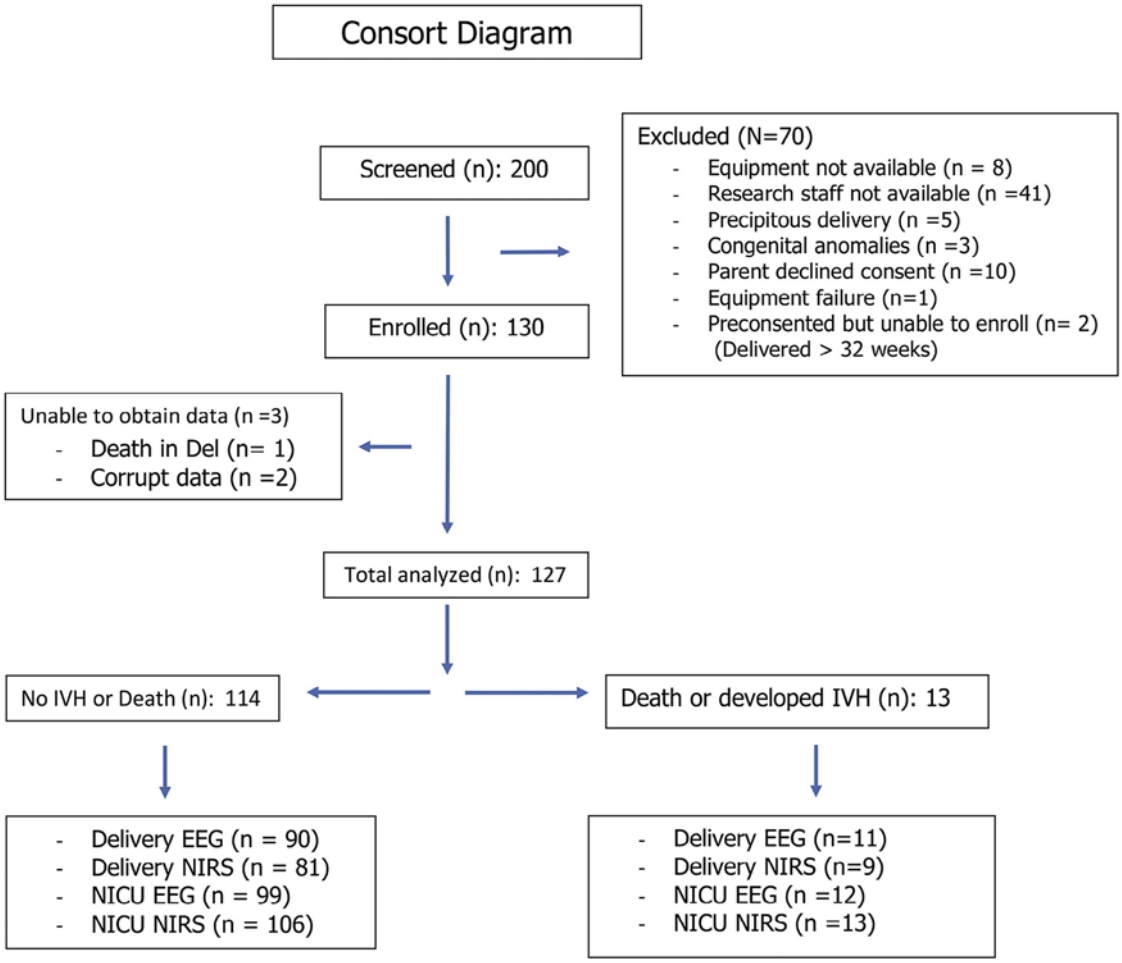

Figure 2. CONSORT diagram.

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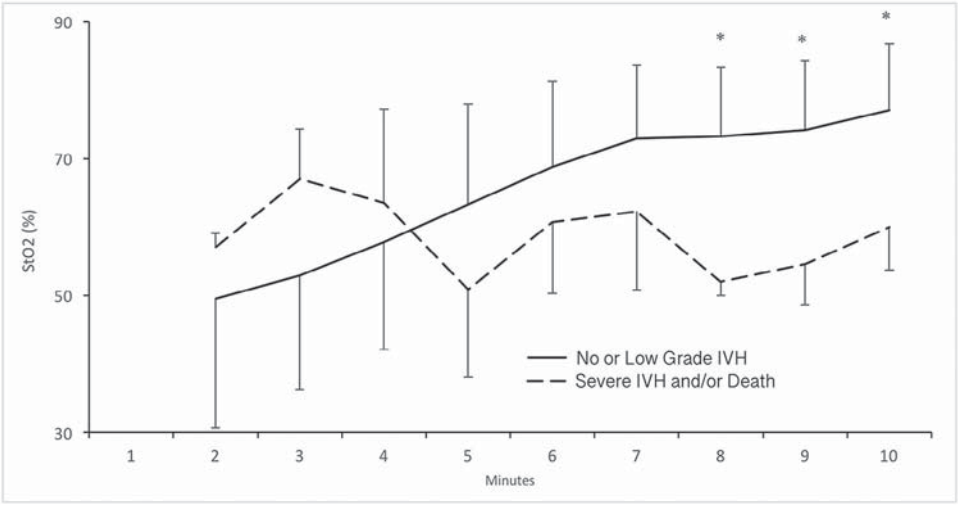

Figure 4. Cerebral StO_2 in the first 10 minutes of life. Subjects with severe IVH and/or death compared with subjects with no or low-grade IVH. *Significance $P < .05$.

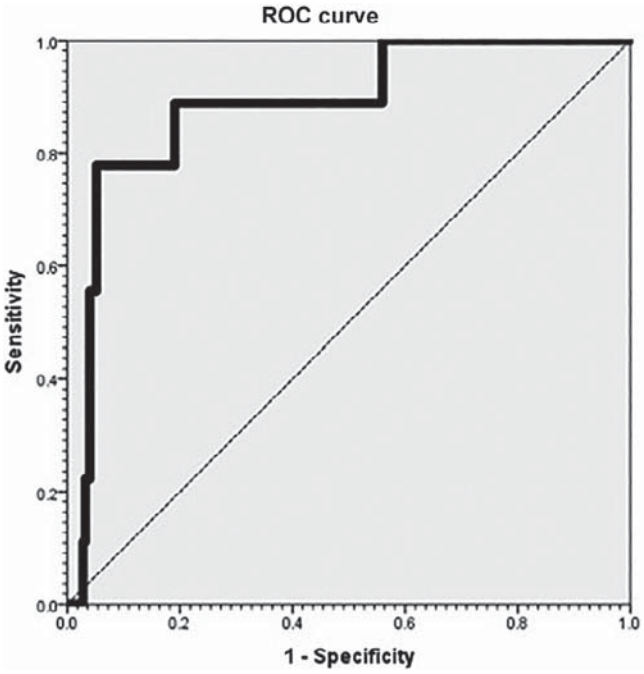

Figure 5. ROC curve for cerebral StO_2 for subjects with severe IVH or death, 7-10 minutes of life (AUC 0.885, $P < .001$, 95% CI 0.775-0.996).

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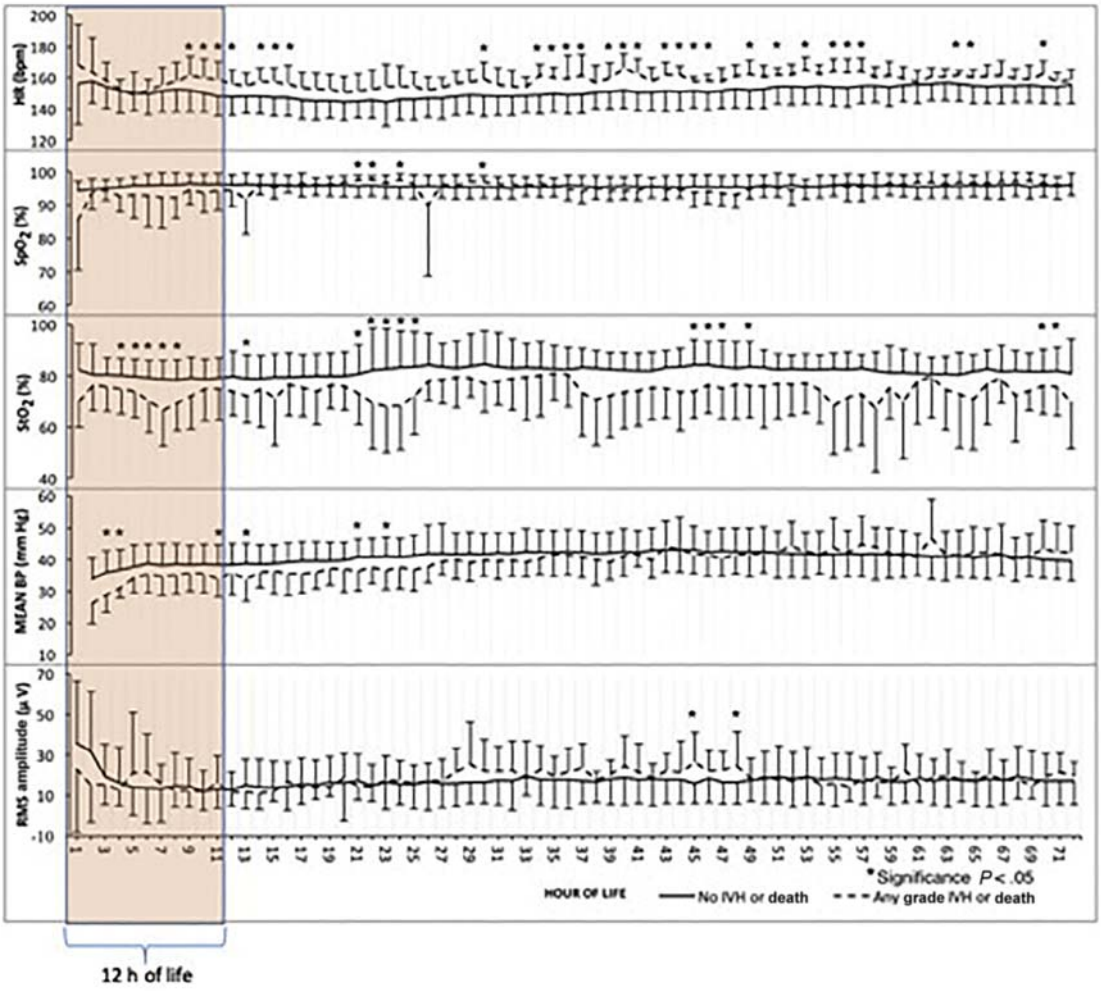

Figure 6. NICU physiologic measurements for the first 72 hours of life. HR, SpO_2, cerebral StO_2, mean arterial blood pressure (mean BP), and single-channel electroencephalogram (RMS amplitude). *Significance $P < .05$.

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