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ORIGINAL ARTICLE

Evolution of early cerebral NIRS in hypoxic ischaemic encephalopathy

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Abstract

Aim: To describe early cerebral oxygenation (cSO_2) and fractional tissue oxygen extraction (FTOE) values and their evolution over the first days of life in infants with all grades of hypoxic-ischaemic encephalopathy (HIE) and to determine whether cSO_2 and FTOE measured early (6 and 12 h) can predict short-term outcome.

Methods: Prospective, observational study of cerebral near-infrared spectroscopy (NIRS) in infants >36 weeks' gestation with HIE. Ten one-hour epochs of cSO_2 and FTOE were extracted for each infant over the first 84 h. Infants with moderate and severe HIE received therapeutic hypothermia (TH). Abnormal outcome was defined as abnormal magnetic resonance imaging (MRI) and/or death.

Results: Fifty-eight infants were included (28 mild, 24 moderate, 6 severe). Median gestational age was 39.9 weeks (IQR 38.1–40.7) and birthweight was 3.35 kgs (IQR 2.97–3.71). cSO_2 increased and FTOE decreased over the first 24 h in all grades of HIE. Compared to the moderate group, infants with mild HIE had significantly higher cSO_2 at 6 h ($p = 0.003$), 9 h ($p = 0.009$) and 12 h ($p = 0.032$) and lower FTOE at 6 h ($p = 0.016$) and 9 h (0.029). cSO_2 and FTOE at 6 and 12 h did not predict abnormal outcome.

Conclusion: Infants with mild HIE have higher cSO_2 and lower FTOE than those with moderate or severe HIE in the first 12 h of life. cSO_2 increased in all grades of HIE over the first 24 h regardless of TH status.

KEYWORDS
cerebral oxygenation, HIE, hypoxic ischaemic encephalopathy, near-infrared spectroscopy, NIRS

Abbreviations: CBF, cerebral blood flow; cSO_2, cerebral oxygenation; EEG, electroencephalography; FTOE, fractional tissue oxygen extraction; HIE, hypoxic ischaemic encephalopathy; MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy; TH, therapeutic hypothermia.

1 | BACKGROUND

Hypoxic ischaemic encephalopathy (HIE) is one of the leading causes of acquired brain injury in term infants.[1] Although therapeutic hypothermia (TH) has significantly improved outcomes in infants with moderate and severe grades of HIE, approximately 40% of infants continue to have adverse neurodevelopmental outcomes.[2] Growing evidence suggests that infants with mild HIE are also at risk of disability.[3]

Alterations in cerebral blood flow (CBF) and metabolism are pathognomonic of HIE. Initially low following the acute HI injury, CBF increases over the first 24 h. Near-infrared spectroscopy (NIRS) monitoring in HIE has many theoretical benefits as it provides continuous, non-invasive monitoring of tissue oxygenation. Cerebral oxygen saturation (cSO_2) may provide useful information on cerebral haemodynamics and can be used as a surrogate of cerebral perfusion.[4] Fractional tissue oxygen extraction (FTOE) is a measure of oxygen extraction. It allows for further interrogation of the cSO_2 trends by providing information not only on oxygen delivery but also regional oxygen uptake and utilisation and therefore provides further insight into cerebral perfusion.[5]

Many studies have assessed the utility of NIRS in the care of infants with HIE, specifically infants undergoing TH.[6] Increased cSO_2 and lower FTOE beyond 24 h have been associated with adverse outcome. The evolution of values over time is also important as greater magnetic resonance imaging (MRI) injury has been identified in infants with more rapidly increasing cSO_2.[7] However, very few studies have examined the use of NIRS at earlier time points and its evolution over time in the setting of HIE.[8] Furthermore, no study has examined the evolution of cSO_2 in infants with mild HIE. The aim of this study was to describe early cSO_2 and FTOE in infants with all grades of HIE, to examine their evolution over time and determine whether early NIRS values (at 6 and 12 h) are useful in the prediction of MRI outcome and/or death.

> **Key Notes**
>
> - Early, objective biomarkers are required to identify infants with hypoxic-ischaemic encephalopathy (HIE) who may be at risk of brain injury.
> - In our cohort, cerebral oxygenation (cSO_2) increased and fractional tissue oxygen extraction (FTOE) decreased over the first 24 h in all grades of HIE regardless of therapeutic hypothermia status and significant differences were seen between infants with mild and moderate HIE in the first 12 h.
> - Early near-infrared spectroscopy did not predict short-term magnetic resonance imaging outcome; however, correlation with long-term follow-up is required.

2 | PATIENTS AND METHODS

This study was part of a larger prospective observational study conducted in Cork University Maternity Hospital, Ireland (November '17–March '20). Infants with all grades of HIE had multi-modal monitoring including NIRS, electroencephalography (EEG), non-invasive cardiac output monitoring, echocardiography, MRI and blood biomarkers. Ethical approval was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

Infants >36 weeks' gestation at birth admitted to the neonatal unit were eligible for inclusion if they had one or more of the following: an Apgar <5 at 5 min, postnatal resuscitation >10 min, pH <7.1/base deficit >16/lactate >9 mmol on cord or first post-natal blood sample, AND clinically evolving encephalopathy defined as abnormal neurological findings on the modified Sarnat Score.[9] Infants were clinically categorised into grade of encephalopathy (mild, moderate, severe) based on assessment using the modified Sarnat score at 1 h of life.[10,11]

Therapeutic hypothermia was provided to infants with moderate and severe grades of encephalopathy. Infants with mild HIE were not cooled. It is practice in our unit that infants undergoing TH receive low dose morphine infusion (10-20 mcg/kg/h) which is titrated to clinical response.

2.1 | Monitoring cerebral oxygenation

Following enrolment, cerebral NIRS monitoring commenced as soon as possible after delivery using the INVOS 5100 and the neonatal OxyAlert™ NIRSensor (Covidien) on the right frontal area. Continuous measurements were recorded during the inpatient stay for up to 4 days where feasible. SpO_2 was measured with the Nellcor SpO_2 Neonatal Sensor (Covidien) and the IntelliVue MP70 (Philips Healthcare) and stored with the EEG signals using NicoletOne EEG (Natus) or Nihon Kohden (Nihon Kohden). Five infants with mild HIE did not have SpO_2 values stored so FTOE was not available.

One-hour epochs of cSO_2 and corresponding SpO_2 were selected at 6, 9, 12, 18, 24, 36, 48, 72 and 84 h of life for each individual infant. FTOE was then calculated using the following standard formula (SpO_2 -cSO_2)/SpO_2 for each infant. For each infant, median cSO_2 and FTOE values across each hour (6, 9, 12, 18, 24, 36, 48, 72 and 84 h) were calculated.

2.2 | Outcome

MRIs were graded using the Barkovich classification by a neuroradiologist and a neonatal neurologist (BW, MM) blinded to grade.[12] Abnormal outcome was defined as abnormal MRI and/or death in the first week. cSO_2 and FTOE were assessed at 6 and 12 h for their ability to predict outcome. These timepoints were selected due to their clinical significance as TH should be commenced within 6 h but infants may still benefit up to 12 h.[2,13,14]

2.3 | Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version 26.0, IBM Corp.) and Stata (version 13.0, StataCorp LP.). Longitudinal mixed models[15] were used to investigate changes in cSO_2 and FTOE over time (from 6 to 24 h after birth) in infants with moderate HIE compared to infants with mild HIE. The optional functional form of the trajectory over time was identified from the family of polynomial functions (a straight line, a quadratic curve and a cubic curve). A bottom-up strategy was used, starting with an empty random intercepts model and then adding each fixed effect (linear, quadratic, cubic) followed by its corresponding random time effect (linear, quadratic, cubic), in turn. Model fit was evaluated using the deviance statistic (−2 log likelihood) and the Akaike Information Criterion. To investigate if changes over time differed by HIE group, the fixed effects of HIE group and the interactions of HIE group by time (linear, quadratic and cubic, as appropriate) were added to the mixed model in a sequential manner. All tests were two-sided and *p*-values <0.05 were considered statistically significant.

Five infants in our cohort had a single seizure during 1 of the included time points. Three had severe HIE and therefore were not included in the mixed model analysis. The 2 included seizures were brief (seizure burden of <5 min/h). Analysis was performed both with and without the infants. There was no difference in the overall results and as their values were similar to other infants in their group, they were included in the final analysis.

To assess prediction of outcome, cSO_2 and FTOE were assessed for their ability to predict abnormal outcome at both 6 and 12 h using the Mann–Whitney *U* test. Likelihood Ratio for a Positive Test (LR[+]) was calculated using the standard formula: Sensitivity/(1 − Specificity), with a LR+ of >10 considered a significant increase in the probability of the outcome. Likelihood Ratio for a Negative Test (LR[−]) = (1 − Sensitivity)/Specificity, with LR− of <0.1 ruling out chance that the infant will have the outcome.[16]

3 | RESULTS

3.1 | Study participants

Fifty-eight infants were included in the analysis (28 mild, 24 moderate, 6 severe). The median gestational age across the entire group was 39.9 weeks (IQR 38.1–40.7) and median birthweight was 3.35 kgs (IQR 2.97–3.71). Demographic information according to grade of HIE is illustrated in Table 1.

3.2 | Summary measures of cSO_2 and FTOE over time

Table 2 displays summary measures of cSO_2 and FTOE over time in all infant groups at all time points. Values ≥95% accounted for 12% of the overall data and were included as 95%. Figure 1 depicts changes in mean cSO_2 and FTOE over time in all infant groups. In all grades, cSO_2 increases and FTOE decreases over the first 24 h and then plateau.

3.3 | Evolution of cSO_2 over time

Mean cSO_2 increased in both the mild and moderate groups over time with the rate of increase slowing down over time (decelerating positive curves) (Figure 2A). The fitted curves were $79.298 + 0.796 \times (\text{hours-6}) - 0.030\,(\text{hours-6})^2$ for the mild group and $71.189 + 1.328 \times (\text{hours-6}) - 0.030\,(\text{hours-6})^2$ for the moderate group. The instantaneous linear rate of change at 6 h after birth was significantly higher in the moderate group (1.328 vs. 0.796 mild, $p < 0.001$). The rate of deceleration in both groups was not significantly different ($p > 0.05$ for group × $[\text{time-6}]^2$ interaction and hence not included in final model). Mean cSO_2 was significantly higher in the mild group compared to the moderate group at 6 h (difference in means [95% CI]: 8.1% [2.7%–13.5%], $p = 0.003$), 9 h (difference in means [95% CI]: 6.5% [1.6% to 11.4%], $p = 0.009$) and 12 h (difference in means [95% CI]: 4.9% [0.4% to 9.4%], $p = 0.032$). No significant differences were found between the two groups at 18 h (difference in means [95% CI]: 1.7% [−2.3% to 5.7%], $p = 0.401$) and 24 h (difference in means [95% CI]: −1.5% [−5.6% to 2.6%], $p = 0.481$).

3.4 | Evolution of FTOE over time

Mean FTOE deceased over time in both groups (Figure 2B). The fitted lines were FTOE = 0.171–0.002 × (hours-6) for the mild group and FTOE = 0.250–0.007 × (hours-6) for the moderate group. The rate of change was faster in the moderate group (−0.007 vs. −0.002 mild, $p = 0.003$) with bigger differences between the 2 groups at the earlier time points. Based on the fitted lines, mean FTOE was significantly higher in the moderate group compared to the mild group at both 6 h (difference in means [95% CI]: 0.079 [0.014 to 0.143], $p = 0.016$) and 9 h (difference in means [95% CI]: 0.064 [0.007 to 0.121], $p = 0.029$). No significant differences were found between the two groups at 12 h (difference in means [95% CI]: 0.049 [−0.002 to 0.099], $p = 0.060$), 18 h (difference in means [95% CI]: 0.018 [−0.024 to 0.060], $p = 0.393$) and 24 h (difference in means [95% CI]: −0.012 [−0.054 to 0.030], $p = 0.571$).

3.5 | Ability of early cSO2 and FTOE to predict MR outcome

Twenty-two percent of infants with mild HIE, 29% of those with moderate HIE and 83% of infant with severe HIE had an abnormal outcome. Two infants died prior to MRI. cSO_2 and FTOE assessed at both 6 and 12 h did not predict abnormal outcome (*p*-values 0.6–0.8).

TABLE 1 Demographics of infants included in study

	Mild *n* = 28	Moderate *n* = 24	Severe *n* = 6
Median (IQR)			
Gestational age (weeks)	40.1 (38.2–40.8)	39.3 (37.8–40.4)	40.4 (39–40.8)
Birthweight (kg)	3.36 (3.04–3.77)	3.29 (2.85–3.63)	3.51 (3.37–3.84)
Lowest pH	7.01 (6.92–7.08)	6.88 (6.81–7.09)	7.05 (6.78–7.12)
n (%)			
Mode of delivery			
Spontaneous vaginal delivery	7 (25)	7 (29)	3 (50)
Instrumental	11 (39)	8 (33)	0
Emergency caesarean section in labour	8 (29)	6 (25)	3 (50)
Emergency caesarean section not in labour	2 (7)	3 (13)	0
Apgar score at 5 min			
0–4	3 (11)	12 (50)	6 (100)
5–7	8 (29)	11 (46)	0
8–10	17 (61)	1 (4)	0
Resuscitation			
Facial O_2	1 (4)	0	0
Positive pressure ventilation	14 (50)	8 (33)	0
CPAP	2 (7)	5 (21)	0
Intubation	1 (4)	5 (21)	2 (33)
CPR	2 (7)	5 (21)	1 (17)
Adrenaline	0	1 (4)	3 (50)
Seizures (EEG)	1	2 (8)	4 (67)
Medication			
Anti-seizure medication	0	3 (13)	4 (67)
Sedation (morphine)	0	24 (100)	6 (100)

At 6 h:

- cSO_2 had a LR+ 1.4 and a LR− 0.5 with a positive predictive value (PPV) of 45% and a negative predictive value (NPV) of 77%
- FTOE had a LR+ 1.3, LR− 0, PPV 46% and NPV 100%

At 12 h:

- cSO_2 had a LR+ 1.3, LR− 0.4, PPV 37% and NPV 86%
- FTOE had a LR+ 1.3, LR− 0, PPV 36% and NPV 100%

4 | DISCUSSION

This study describes the evolution of NIRS in infants with all grades of HIE. Infants with moderate HIE have significantly lower predicted cSO_2 and higher FTOE 6 h after delivery compared to infants with mild HIE who are not cooled, however, by 18 h, there is no difference between the groups. In all infants, cSO_2 increases over the first 12–18 h then plateaus. Although the numbers were small, cSO_2 in infants with severe HIE appears to increase almost linearly over the first 36 h. In both the moderate and severe groups, cSO_2 and FTOE essentially remain unchanged during rewarming.

We do not have control data for this cohort; however, normative values exist in the literature.[17,18] Our values in the moderate and severe groups are above the suggested cSO_2 values of 78% (+/−7) for full term infants on day 1–2 of life using the same device and probe. Studies have also demonstrated a gradual decrease in cSO_2 over the first 120 h.[18] In our cohort, cSO_2 increases in all groups over the first 20 h, suggesting that encephalopathy alone, regardless of TH, may have an early effect on cerebral oxygenation.

Both animal and clinical studies have shown that the severity of the underlying encephalopathy has a major influence on CBF.[19,20] In HIE, CBF is initially low and increases over the first 24 h likely due to a disruption in haemodynamic control.[21] Whether this initial hypoperfusion is a protective strategy to reduce metabolic demand and thus further brain injury or whether it is as a result of neuronal injury and death is unclear.[22] HIE may also result in impaired ventricular function secondary to ischemia which may further compound cerebral perfusion.[23] Wintermark et al. found that infants with brain

TABLE 2 Summary measures of cSO_2 and FTOE over time by group

	Overall			Mild HIE—Uncooled			Moderate HIE—Cooled			Severe HIE—Cooled		
Hours of age	*n*	Mean	(SD)	*n*	Mean	(SD)	*n*	Mean	(SD)	*n*	Mean	(SD)
cSO_2												
6	33	75.6	(10.0)	15	77.6	(9.0)	15	74.0	(11.8)	3	73.3	(1.5)
9	49	78.2	(9.5)	24	80.8	(7.1)	21	74.9	(11.6)	4	79.8	(5.4)
12	55	80.6	(8.9)	26	83.3	(7.7)	24	77.5	(9.8)	5	81.4	(6.8)
18	56	83.5	(8.0)	27	84.6	(7.5)	24	83.0	(8.4)	5	80.2	(9.8)
24	52	84.9	(7.3)	24	83.9	(7.5)	23	85.5	(7.4)	5	86.8	(7.0)
36	36	87.8	(6.4)	7	88.1	(5.9)	23	86.8	(6.6)	6	91.0	(5.9)
48	30	88.7	(6.1)	2	84.0	(1.4)	23	88.9	(6.2)	5	89.8	(7.1)
72	27	87.0	(7.4)	0			23	87.5	(7.2)	4	84.0	(9.1)
84	26	87.2	(7.7)	0			22	87.3	(7.4)	4	87.0	(10.9)
FTOE												
6	26	0.22	(0.10)	11	0.21	(0.10)	12	0.22	(0.11)	3	0.24	(0.03)
9	38	0.21	(0.10)	17	0.18	(0.07)	18	0.24	(0.12)	3	0.19	(0.07)
12	46	0.18	(0.10)	21	0.16	(0.09)	21	0.21	(0.10)	4	0.13	(0.08)
18	47	0.15	(0.07)	22	0.15	(0.06)	22	0.16	(0.08)	3	0.13	(0.09)
24	42	0.14	(0.07)	19	0.14	(0.06)	20	0.14	(0.07)	3	0.14	(0.08)
36	28	0.11	(0.07)	5	0.11	(0.07)	19	0.12	(0.07)	4	0.07	(0.08)
48	24	0.11	(0.07)	2	0.14	(0.02)	19	0.11	(0.07)	3	0.11	(0.10)
72	23	0.12	(0.08)	0			19	0.12	(0.08)	4	0.13	(0.11)
84	22	0.11	(0.09)	0			18	0.11	(0.08)	4	0.08	(0.14)

Abbreviations: FTOE, fractional tissue oxygen extraction; HIE, hypoxic-ischaemic encephalopathy.

injury on MRI displayed hypoperfusion on day 1, followed by hyperperfusion on days 2–3 and early hyperperfusion had an increased risk of brain injury.[19] Our results infer similar findings; infants with moderate HIE have lower cSO_2 initially compared to the mild group and infants with moderate and severe HIE have increasing cSO_2 values beyond 20 h of life. It would appear that the severity of encephalopathy has an independent impact on cerebral oxygenation. The rate of change may also be important. Wintermark et al.[24] showed that a greater increase in cSO_2 was seen in infants with severe HIE compared with those with moderate HIE. This is true of our cohort. Infants with moderate HIE had a greater rate of increase in cSO_2 compared to the mild group and although inferential statistics were not possible in the severe group, their mean values suggest values higher than the moderate group.

Therapeutic hypothermia is an important factor to consider as in our cohort, infants with moderate–severe HIE received TH while infants with mild HIE did not. The goal of TH treatment in HIE is to reduce cerebral metabolism which results in decreased oxygen consumption. FTOE values in the mild group decrease slightly but generally remain stable over time. In the moderate group receiving TH, predicted FTOE values are significantly higher than the mild group during the first 9 h but by the end of the first day, FTOE values are similar to that of the mild group and continue to decrease further with cSO_2 increasing accordingly. By 24 h, there is a trend towards a lower FTOE and higher cSO_2 in the moderate group. Although grade of encephalopathy plays an important role initially by determining the 'starting points', TH may have a protective effect on cerebral metabolism. Concerns have been raised that TH may also have an effect on reducing brain blood flow, specifically via resulting bradycardia, which may result in reduced cardiac output and subsequent decrease in oxygen delivery.[2,25] Furthermore, pCO_2 has a significant influence on the cerebral vasculature. Hypothermia affects our ability to accurately measure pCO_2 thus raising concerns that pCO_2 in infants may be lower than assumed resulting in vasoconstriction and reduced CBF.[26] However in our cohort, cSO_2 and FTOE remain relatively stable beyond the first day and during the rewarming period in the moderate and severe groups. This suggests preserved CBF.

Sedation is routinely used in our unit for infants receiving TH. Seven infants also received anti-seizure medication for the treatment of seizures. Studies have demonstrated a decrease in FTOE following administration of sedative medication.[27] In our practice, sedation is maintained at the lowest dose required to ensure comfort and is routinely weaned and discontinued towards the end of the TH and during rewarming. Again, no change in cSO_2 or FTOE were noted at this time suggesting minimal effect of the sedation.

Objective, reliable biomarkers are required to identify infants at risk of brain injury in the crucial 6 h therapeutic window as current

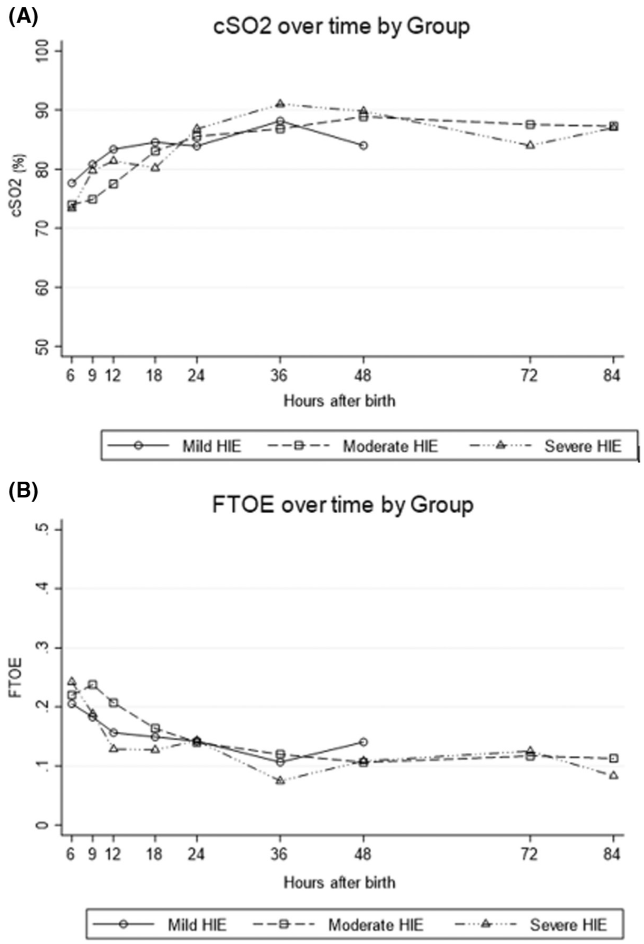

FIGURE 1 Mean cSO_2 (A) and FTOE (B) for each HIE group at each time point. cSO_2, cerebral oxygenation; FTOE, fractional tissue oxygen extraction; HIE, hypoxic-ischaemic encephalopathy

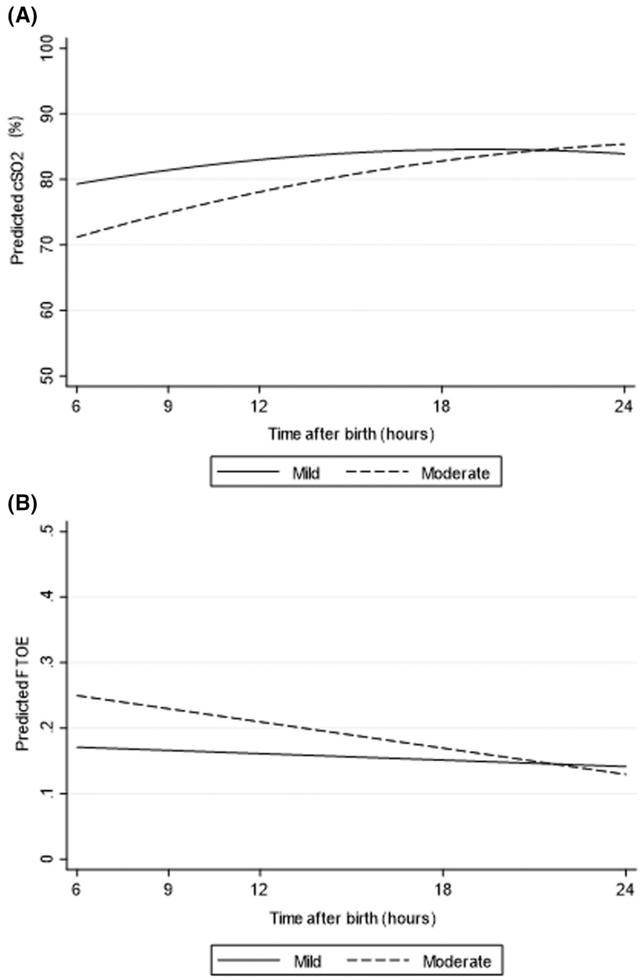

FIGURE 2 Predicted cSO_2 (A) and FTOE (B) over time by HIE group. cSO_2, cerebral oxygenation; FTOE, fractional tissue oxygen extraction; HIE, hypoxic-ischaemic encephalopathy

methods primarily involve clinical assessment which is subjective and was never validated to examine infants as early as 6 h.[28] Although a number of blood and CSF-based biomarkers are currently under investigation, none are in routine clinical practice.[29] EEG and aEEG play key roles in monitoring infants with HIE. Prior to TH, they were the most useful tools in predicting outcome; however, they are now most predictive of outcome at 24–48 h.[30] NIRS monitoring has many theoretical benefits in HIE as it can detect alterations in cerebral oxygenation and cerebral metabolism; changes which are pathognomonic of HIE. Unlike other monitoring modalities like EEG, which require expert interpretation, NIRS can be applied easily and quickly and can be implemented into clinical care with minimal training.

Beyond 24 h, higher cSO_2 and lower FTOE have been associated with MRI injury and poor neurodevelopmental outcome at 18–24 months.[6] When combined with aEEG, improved prediction of abnormal outcome was possible at 12–36 h of age.[6] However, few studies have examined the ability of early NIRS to predict outcome.[8] We examined the use of NIRS values at 6 and 12 h to predict MRI outcome. cSO_2 and FTOE, either in isolation or combined, did not predict abnormal outcome at these early time points. FTOE at both 6 and 12 h had a LR− of 0, suggesting FTOE may be helpful in ruling out infants with injury; however, further research is warranted. Long-term neurodevelopmental follow-up of our cohort is currently underway.

This study is limited by the small number of infants included particularly in the early time measurements and the varying number of data available at each time point. Obtaining early data in this cohort is challenging.[8] Only 26 infants were included at 6 h; however, these numbers are similar to previously published studies examining NIRS at this early time point.[8] We do not have a control group, however, data from healthy term controls have been published previously as discussed above. A well-documented limitation of the INVOS neonatal sensor is that it truncates values to between 15% and 95%. We are therefore unable to describe values above 95%, which may have limited our ability to distinguish between groups. In addition, data beyond 24 h are limited for infants with mild HIE and therefore we cannot determine the clinical significance of NIRS values beyond this time frame.

This study provides novel, early NIRS data in all grades of HIE and its evolution over time. In all grades, cSO_2 increases over the first 24 h with a resultant decrease in FTOE. Although significant differences are evident between the uncooled mild group and the infants with moderate HIE receiving TH at the earlier time points, by 12 h there is no difference in oxygen uptake and cSO_2 are similar by 18 h. While cSO_2 values in the mild group lie within suggested normative ranges, the trend of an increasing cSO_2 over time is different to previously published normative data suggesting an effect of the underlying encephalopathy itself.[17,18] Early cSO_2 and FTOE were not helpful in the prediction of short-term outcome. Further research on this group is required and correlation with long-term outcome is essential to determine whether early NIRS is helpful in the identification of infants at risk of brain injury.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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