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Serial aEEG recordings in a cohort of extremely preterm infants: feasibility and safety

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Abstract

Introduction—Amplitude-integrated EEG (aEEG) monitoring is increasing in the neonatal population, but the safety and feasibility of performing aEEG in extremely preterm infants have not been systematically evaluated.

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CONFLICT OF INTEREST

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Methods—Inborn infants $23^{0/7}$ – $28^{6/7}$ weeks gestation or birth weight 401–1000 grams were eligible. Serial, six-hour aEEG recordings were obtained from first week of life until 36 weeks postmenstrual age. Adverse events were documented, and surveys evaluated the impact of the aEEGs on routine care. Success of performing aEEGs according to protocol and aEEG quality were assessed.

Results—102 infants were enrolled, with 755 recordings performed. 83% of recordings were performed according to schedule, and 96% were without adverse event. Bedside nurses reported no interference with routine care for 89% of recordings. 92% of recordings had acceptable signal quality.

Conclusions—Serial aEEG monitoring is safe in preterm infants, with few adverse events and general acceptance by nursing staff.

Introduction

Amplitude-integrated electroencephalography (aEEG) was first introduced in the 20th century as a tool for intra-operative and intensive care monitoring of brain function in adults.[1] The technology has gained acceptance in the neonatal intensive care nursery (NICU), first in Europe and more recently in the United States.[2, 3] aEEG has become a common method of neuromonitoring due to its ease of use, minimal interference with clinical care, and limited training requirements for interpretation. Research first focused on the use of aEEG to screen for seizure activity[4] and to assist in the prediction of outcome in term infants with hypoxic-ischemic encephalopathy (HIE).[5, 6, 7] aEEG has been used widely to identify candidates for therapeutic hypothermia.[5, 7, 8, 9]

Premature infants are at high risk for neurodevelopmental disabilities, and aEEG may provide information regarding cerebral function that may be a useful early adjunct to findings on cranial ultrasound or magnetic resonance imaging. Initial studies in preterm infants indicate potential for aEEG to aid in prognostication of early childhood outcomes.[10, 11, 12] Most studies of aEEG in preterm infants have been conducted in single centers with particular expertise in performing the technique, however, and aEEG has not necessarily been incorporated as a routine neuromonitor in preterm infants. In 2008, a survey of 15 academic centers in the United States found that only one center was conducting research using aEEG in preterm infants with post-hemorrhagic hydrocephalus, and another was using it routinely for cerebral maturation (data unpublished). Concern about the performance of aEEG in this medically fragile population focused on the potential for respiratory instability and skin fragility associated with aEEG electrode application.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) developed a pilot protocol to study the feasibility of performing aEEG recordings in extremely preterm (EPT) infants with an eventual goal of investigating the ability of aEEG to predict early childhood outcomes in preterm infants. In particular, we sought to assess: 1, the ability to enroll extremely preterm infants <29 weeks gestational age or ≤1000 grams; 2, the success of performing aEEGs in the first week of life and weekly until 36 weeks postmenstrual age (PMA); 3, the quality of the aEEG recordings using hydrogel electrodes placed by research staff; and 4, the impact of

aEEG recordings on routine clinical care and adverse events as a result of the aEEG technique.

Methods

Patient population

This study was conducted from July 2009 through June 2010 in 7 NRN centers (Brown University, Duke University, Emory University, Stanford University, University of Texas-Southwestern, University of Texas-Houston, and Wayne State University). Inborn infants with a gestational age (GA) $23^{0/7}$ – $28^{6/7}$ weeks or with a birth weight (BW) 401–1000 grams were eligible for this study. With a primary aim of assessing the feasibility of performing early aEEG recordings, enrollment was required prior to 72 hours of age. Exclusion criteria included: non-intact skin involving the central or parietal regions of the scalp; known or suspected congenital anomalies such as central nervous system malformations, chromosomal anomalies or multiple congenital anomalies, complex congenital heart disease, or inborn error of metabolism; or terminal illness (pH<6.8 for >2 hours or persistent bradycardia [heart rate < 100 beats per minute] associated with hypoxia for > 2 hours). Institutional Review Board approval was obtained at each of the 7 NRN sites. The protocol was submitted to the Federal Drug Administration, which deemed that an Investigational Device Exemption was not necessary. It was also reviewed and approved by the independent NRN Data Safety and Monitoring Committee (DSMC).

Data collection and study definitions

Eligible infants were concurrently enrolled in the NRN Survey of Morbidity and Mortality among High Risk Preterm Infants, a registry of demographic, perinatal, and neonatal outcome data of early gestational age infants. Data were collected by trained research staff from birth until death, hospital discharge, or 120 days using definitions common to NRN publications.[13, 14]

aEEG recordings

Study technique—Prior to study initiation, the Principal Investigator (PI) conducted training visits at all study centers to instruct the research staff in the placement of hydrogel aEEG electrodes. These sessions also reviewed how to handle the infant and permit parent holding without disrupting electrodes. aEEG recordings were performed using the BrainZ BRM3 monitor (Natus Medical Incorporated, San Carlos, CA) with hydrogel electrodes (Micro Neoleads, Neotech Products, Valencia, CA or Natus Neonatal Sensors, Natus Medical Incorporated, San Carlos, CA). Leads were placed at C3, C4, P3, and P4 according to the international 10–20 system and a ground electrode was placed on the back. Skin preparation was individualized to the patient based on assessment of skin integrity, and ranged from cleaning and gentle abrasion with a moistened cotton swab to use of an exfoliant (NuPrep, Weaver and Company, Aurora, CO), and/or application of a small amount of conductive paste (Ten20, Weaver and Company) as needed to achieve an impedance <7.5kΩ. Research staff monitored the impedance at the initiation and at the mid-point of the recording. At the recommendation of the DSMC, the BRM3 displayed the

impedance screen during the recording and the clinical team was masked to the aEEG tracing.

aEEG recording schedule—To assess the maturation of aEEG recordings with advancing postnatal age, serial six-hour aEEGs were obtained. Two aEEG recordings were performed in the first week of life: one between birth and 72 hours, and the second between 72 and 168 hours (7 days), with a minimum of 72 hours between recordings. Weekly recordings were performed thereafter (with 4 – 10 days between recordings) until 36 weeks PMA, transfer to a non-study center, or discharge, whichever came first.

Feasibility, safety and clinical acceptance measures

Reasons for non-enrollment and non-adherence to the aEEG recording schedule were documented. For each aEEG recording, bedside nurses were asked to complete a questionnaire during or just following their shift about the impact of the aEEG monitoring on routine care and to note procedures that were delayed as a result of study participation (see Supplemental material). The survey was comprised of two questions to determine: 1) a qualitative assessment of the perceived impact of the aEEG on patient care, and 2) activities delayed as a result of the aEEG recording, including kangaroo care/parent holding, and the duration of the delay. Research personnel subsequently coded these events for the purposes of analysis.

Adverse events were documented by research staff, including detailed information about skin complications, device-related events, and other patient complications (e.g. accidental extubation, bradycardia, desaturation, hypothermia). For skin breakdown issues, information about the size of the area affected, the time to resolution, and any need for intervention was collected. The DSMC reviewed adverse events after 45 patients (approximately half of target enrollment)had been enrolled and concluded there were no safety concerns.

aEEG interpretation

Files were downloaded from the BRM3 unit by research staff and transmitted to the NRN Data Coordinating Center at RTI International for central reader interpretation. Central reading of aEEG is the basis of a subsequent report. Recordings were assessed using an offline analysis software (Analyze Research v1.5). The cross-cerebral channel (P3-P4) was assessed for signal quality, defined by an impedance <7.5kΩ and absence of external signal artifact. The cumulative time for areas of acceptable tracing was summed, up to a maximum of 6 hours. Bedside nurses were able to enter clinical events into the monitor, such as routine care/handling, suctioning, intubation, surfactant administration. The aEEG reader was masked to other patient clinical information and outcomes.

Statistical analysis

For the purposes of a subsequent analysis to compare aEEG interpretations by length of recording, sample size calculations were based on the ability to detect sleep-wake cycles with 3-hour vs.6-hour recordings, assuming a higher false-negative rate (FNR) for a shorter recording. Sample sizes necessary to detect a difference in FNR between 3-hour and 6-hour recordings were calculated for a range of FNRs and the maximum number obtained was 85,

thus, this was the minimum sample size goal. The individual site recruitment goal was a minimum of 10 patients per center in order for research personnel to gain adequate experience with the aEEG technique. Enrollment continued at all sites until the total enrollment was over 85 and each center had at least 10 participants.

Statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute, Cary, NC). Bivariate analyses were conducted to compare the demographic, perinatal, and neonatal characteristics of enrolled vs. non-enrolled infants using Student's *t* tests for continuous variables and χ^2 tests for differences in proportions. Descriptive statistics were generated for rates of enrollment, protocol violations, data signal quality, adverse events, clinical event documentation, and feedback by bedside nurses.

RESULTS

Enrollment feasibility

During the study period, 399 infants were eligible for inclusion in the study and 102 (26%) were enrolled. Reasons for non-enrollment are shown in Figure 1. The average postnatal age at time of enrollment was 32.4hours (standard deviation [SD] 24 hours). Enrollment rates by center varied from 16.5% to 43%. Enrollment increased with advancing GA, from a minimum of 6% for 23 weeks to a maximum of 33% for 28 weeks, but the difference in enrollment rates was not statistically different.

Demographic, perinatal, and neonatal characteristics of enrolled and non-enrolled infants are shown in Table 1. The mothers of enrolled infants were significantly younger and more likely to have less than a high school education and to be recipients of public insurance. Enrolled infants were of higher mean gestational age and birth weight, but these differences were not statistically significant. Respiratory variables were not significantly different between enrolled and non-enrolled infants, with similar rates of ventilation and supplemental oxygen in the first 72 hours of life. Infants not enrolled had a higher rate of death before discharge, though there was not a significant difference in the rate of death prior to 72 hours of life.

Of the 102 enrolled infants, 4 died during the study period, with none of the deaths attributed to study procedures. Parents withdrew consent for 10 infants, and 15 infants were transferred to a non-study site prior to 36 weeks PMA.

Adherence to aEEG recording schedule

The expected number of recordings was 908, based on 2 recordings in the first week of life and weekly recordings thereafter until 36 weeks PMA, death, withdrawal, or transfer (whichever came first). In total, 755 aEEG recordings were performed during the study period (83% of expected). The observed and expected number of aEEG recordings is shown in Table 2 by gestational age and postnatal age. Seventy-five infants (74%) had an aEEG recording in the first 72 hours of life at an average postnatal age of 48.3 hours (SD 14.6 hours). The median age at first aEEG recording among all enrolled infants was 56.6 hours. There were 96 protocol deviations (Table 3), with 27 in the first 72 hours and 15 between 72 hours and 7 days of life. The most common reasons for a missed recording included an

infant being deemed too ill for electrode application (e.g. desaturations with stimulation, high frequency ventilation with the judgment that an infant is too ill) or the infant being in accessible (e.g. in isolation, scalp IV impeding proper electrode placement). Although the single 23-week GA infant did not have a recording until week 5, there were no significant differences in the rate of recordings in the first week of life or during the entire study period when infants ≤ 25 weeks GA were compared to infants ≥ 26 weeks GA; a similar result was found when the cohort was analyzed using a cut off of 24 weeks GA.

aEEG recordings quality

Of the 755 recordings performed for this study, 747 (99%) were assessed for signal quality. Eight recordings were unavailable for review, either due to being lost or file corruption in the transmission process. Ninety-two percent of recordings were of adequate quality for at least 5.5 hours to permit assessment of background voltage pattern, and 99% permitted at least a 3-hour assessment.

Impact on clinical care and adverse events

Bedside caregiver surveys were returned for all but one of the 755 aEEG recordings performed. Nurses reported that the aEEG did not interfere with their ability to provide patient care for 89% percent of recordings, and that it interfered “somewhat” with their ability to care for the infant for 10% of recordings (n=78). The aEEG interfered “significantly” with patient care in 1% of recordings (n=6), and reasons included (more than one answer possible): infant became cold (n=2), poor IV access and unable to start scalp IV (n=1), not tolerating stimulation (n=1), nasal prongs falling out (n=2), and accessibility concerns (n=1). Clinical procedures delayed as a result of aEEG recording were reported in 20 instances, all but one delayed by less than one hour. Parent holding was reported as being delayed by 15–30 minutes in 2 instances.

Adverse events that were “possibly” or “probably” related to study procedures were reported in 6 (6%) of enrolled infants (Table 3), or less than 1% of all recordings. These events included self-resolved skin breakdown (3), accidental hair removal by hydrogel electrodes (1), cold stress, defined as temperature <36°C (1), and desaturation events (1). While not recognized as an adverse event, skin irritation was reported in 28 (4%) of recordings, all of which self-resolved, the majority (19) in less than 24 hours. Of these events, erythema comprised the majority of occurrences (21), followed by abrasion (6), and one episode of both erythema and abrasion.

DISCUSSION

There is growing interest in the ability of aEEG measures to predict short-term and early childhood outcomes in EPT infants, and the body of literature to support the use of this technology is expanding. However, there remains concern about whether the application of electrodes is too invasive for this fragile population. This pilot study of 102EPT infants is the first to systematically report the feasibility of performing aEEG in extremely preterm infants in the context of a multi-center study. Enrollment from the eligible population was lower than expected, with equipment and personnel availability proving to be significant

constraints. Consent was granted by just under half of parents who were approached, and withdrawal occurred in nearly 10% of enrolled infants. This was an observational study of a novel NICU monitoring device, and both of these variables likely reflect the fact that there was no direct benefit to study participation, as the clinicians could not view the aEEG recordings and provide feedback to parents. Further, there are potentially important differences between enrolled and eligible, non-enrolled infants, with lower socioeconomic status in the enrolled group. Overall protocol adherence, data signal quality, and caregiver acceptance were good.

Much of the literature on aEEG in preterm infants has focused on establishing reference values in healthy cohorts[15, 16, 17, 18, 19, 20] or exploring aEEG measures that are associated with normal early childhood outcomes.[21, 22] In studies of sick preterm infants or in infants with intracranial pathology, many authors report only the number of infants enrolled and have not stated consent rates or described their non-enrolled population.[23, 24, 25, 26] Our study provides data that will inform investigators for future research on aEEG in preterm infants with respect to estimating sample size and the resources required to recruit subjects in light of the low consent rate. Published enrollment data reflect variable consent rates. Inder et al. reported an enrollment rate of 87% in a population of 59 very low birth weight (VLBW) infants with a median GA of 27 weeks.[27] Shah et al. studied infants <30 weeks GA, with 47% consent rate.[28] Heldermanet al. studied infants <28 weeks GA and enrolled 48% of eligible infants.[29] El-Dib et al. studied 100 VLBW infants with a mean GA of 27.9 weeks and reported a consent rate of 89%.[12] More recently, West et al. published a cohort of 76 infants less than 29 weeks GA, with a consent rate of 70%.[11] Most of these studies were performed in a single center and differed from ours in that only a single recording was obtained in the first few days of life. In the Austrian cohort, where serial recordings of infants < 30 weeks GA were performed, Olischar et al. reported the investigation of a "consecutive series" of 56 infants with intraventricular hemorrhage,[30] and Klebermass et al. reported that aEEGs were obtained on "all infants born" during the study period.[10] Studies with higher consent rates were often performed outside the United States, where aEEG monitoring is more often performed as part of routine clinical care; it is unclear if consent was granted for electrode application or just abstraction of aEEG data.[31, 32]

The aforementioned studies also did not provide data regarding the safety of the aEEG technique in the fragile EPT population. A separate study assessed skin fragility issues with hydrogel electrodes in 16 medically-stable preterm infants and found no report of skin irritation, though enrollment was limited to older gestational ages (31–36 weeks).[33] In our study, there was a dedicated effort by investigators through on-site instruction using NICU patients, many of whom were critically ill and on ventilators. This ensured that research staff were trained in the technique of skin preparation for hydrogel electrode application and likely facilitated the low rates of serious adverse skin events, which was one of the primary concerns expressed by NRN PIs at the time the study was proposed. The low rate of other adverse events is also likely the result of our training efforts. Thus, in the setting of hands-on training, aEEG can safely be applied to critically ill EPT infants.

The contrast in neuromonitoring practices between Europe and the United States is highlighted by two surveys of aEEG and EEG monitoring in newborns. Boylan et al. queried

210 physicians who were predominantly European (59%) neonatologists (63%), with approximately 72% using aEEG in their NICUs. These data are contrasted with a survey by Glass et al., where 75% of the 193 respondents were from the United States.[4] Approximately 35% used aEEG to diagnose seizures, and aEEG was used in 37% of preterm infants and 43% of term infants at risk for seizures. At the time our study was conducted, only one NRN center was utilizing aEEG for clinical monitoring, mostly in the term HIE population, and another reported limited research use of aEEG in preterm infants. Recruitment success for aEEG research in EPT infants may be heavily influenced by local routine clinical practice.

The 7 NRN centers in this study participated because there were investigators at each site with an interest in aEEG research. However, none had a multidisciplinary, coordinated approach to neuromonitoring at the time of the study. The establishment of dedicated neonatal neurointensive care units is increasing within academic neonatal intensive care units.[2, 34] These units are comprised of a multidisciplinary team of neonatologists, neurologists, neurophysiologists, and neuroradiologists. In this construct, bedside nurses are also provided training in the placement of aEEG electrodes and in basic interpretation methods. This interest in neuromonitoring will enhance the ability to conduct aEEG research and provide real-time assessment of signal quality to ensure adequate tracings. Further, the bedside provider survey data show that the technology is generally accepted by nursing staff, and there should be few barriers to implementation of aEEG technology into routine clinical practice in the future.

A strength of our study is the relatively large number of infants studied with serial aEEG recordings, with an overall protocol adherence rate of 83%. However, if aEEG is to be used as an early biomarker of brain injury and adverse outcome in EPT infants, it will be important to obtain aEEGs on the sickest infants early in their hospital course. Our trend toward lower success rate in recording the younger gestational age infants early in their hospitalization is a limitation of this study. We speculate that increased clinical aEEG use and the data presented in this study will reduce perceived barriers to future study of the sickest, most fragile infants.

This pilot study demonstrates the feasibility of aEEG application in extremely preterm, extremely low birth weight infants with a good safety profile, few adverse events, and acceptance by bedside nursing personnel. These data support the feasibility of aEEG in preterm infants and its continued study to establish the predictive ability of longitudinal assessment toward neurodevelopmental outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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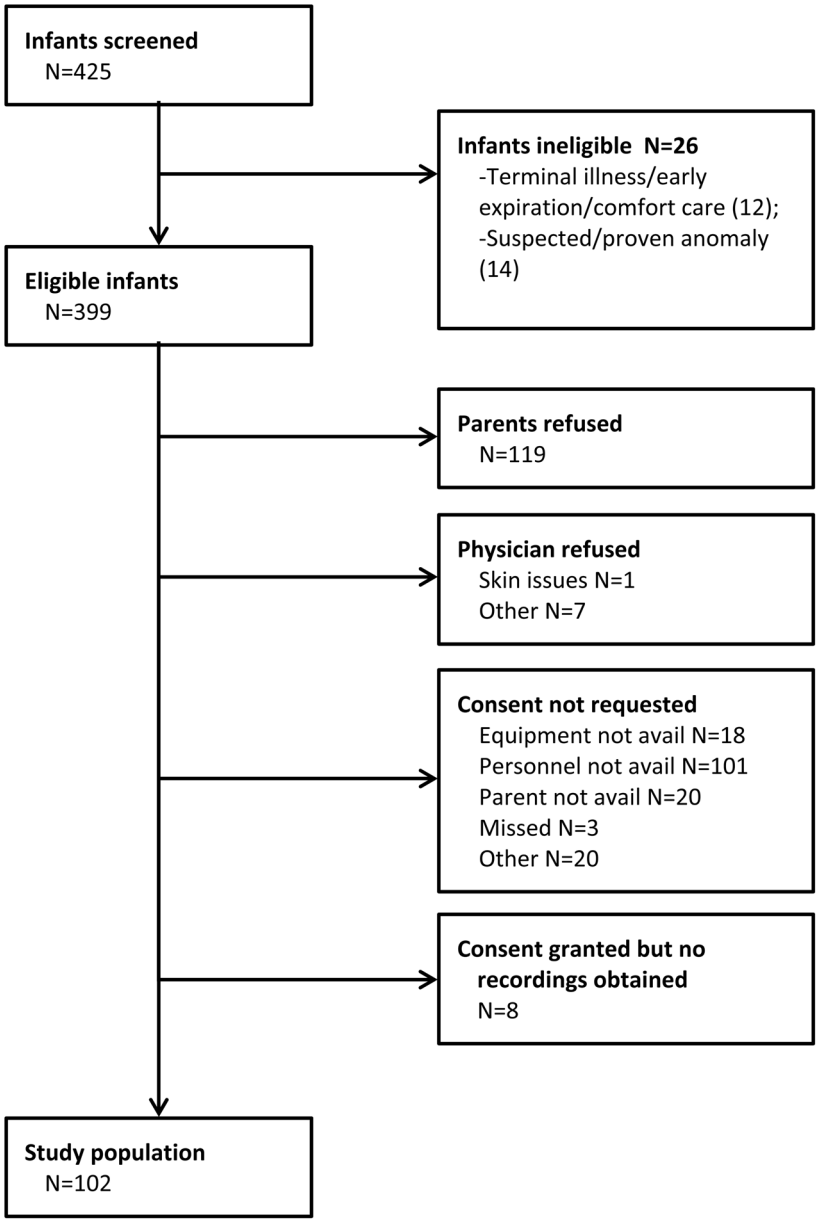

Figure 1.

Patient flow diagram detailing number of infants screened, eligible, enrolled, and reasons for non-consent.

Table 1

Comparison of enrolled vs. non-enrolled patients

Variable*	Enrolled (N=102)	Eligible, Not enrolled (N=297)	P value
Demographic			
Maternal age, years	26 ± 6.5	28.2 ± 5.9	<0.01
Maternal education < high school≠	31 (34)	59 (23)	<0.05
Maternal insurance status			0.03
Private	26 (26)	119 (40)	
Public	72 (71)	165 (56)	
Self-pay/uninsured	3 (3)	8 (3)	
Other	0 (0)	5 (1)	
Maternal race/ethnicity			0.70
White	31 (31)	86 (28)	
Black	40 (39)	106 (36)	
Hispanic	25 (25)	79 (27)	
Other	6 (6)	27 (9)	
Perinatal			
Gestational age, weeks	27.0 ± 1.6	26.7 ± 1.7	0.09
Birth weight, grams	924.4 ± 222	875.4± 235.4	0.07
Small for gestational age	10 (10)	38 (13)	0.42
Male	54 (53)	147 (50)	0.5
Multiple gestation	22 (22)	85 (29)	0.17
Cesarean delivery	73 (72)	210 (71)	0.87
Antenatal steroids	89 (87)	255 (86)	0.78
5-minute Apgar <4	6 (6)	26 (9)	0.36
CPR in delivery room	10 (10)	22 (8)	0.44
Neonatal			
FiO_2 at 24 hours of life	0.29 ± 0.11	0.29 ± 0.13	0.85
On ventilator at 24 hours of life	53 (52)	151 (51)	0.87
High-frequency ventilator in first 72 hours of life	16 (16)	61 (21)	0.34
Early onset sepsis	3 (3)	7 (2)	0.75
Severe IVH or cPVL	22 (22)	48 (16)	0.22
BPD≠	33 (34)	101 (39)	0.44
NEC	6 (6)	21 (7)	0.67
ROP≠	44 (47)	149 (57)	0.09
Death before discharge	6 (6)	41 (14)	0.03

Definitions: severe intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (cPVL), broncho pulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP)

* Data are expressed as mean ± standard deviation for continuous variables and n (%) for categorical variables

≠ Percentages calculated after missing data removed from the denominator, as follows: maternal education (11 enrolled, 46 not enrolled), BPD (6 enrolled, 43 not enrolled), and ROP (8 enrolled, 41 not enrolled).

Table 2

Summary of observed and expected recordings performed according to gestational age and postnatal age

GA (wks)	<72 hours	72–168 hours	Wk 2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12	Wk13	Total
23	0/1 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	7/14 (50%)
24	7/11 (64%)	10/11 (91%)	6/11 (55%)	6/11 (55%)	7/10 (70%)	7/10 (70%)	6/9 (67%)	8/9 (89%)	7/9 (78%)	7/9 (78%)	8/9 (89%)	5/9 (56%)	8/9 (89%)		92/127 (72%)
25	13/16 (81%)	14/15 (93%)	11/14 (79%)	13/14 (93%)	11/13 (85%)	13/13 (100%)	12/13 (92%)	11/13 (85%)	11/11 (100%)	8/10 (80%)	10/10 (100%)	10/10 (100%)			137/152 (90%)
26	11/18 (61%)	13/17 (76%)	13/17 (76%)	13/15 (87%)	15/15 (100%)	13/13 (100%)	10/13 (77%)	11/11 (100%)	9/10 (90%)	10/10 (100%)	8/9 (89%)				126/148 (85%)
27	20/23 (87%)	23/23 (100%)	19/22 (86%)	18/22 (82%)	21/22 (95%)	20/22 (91%)	16/21 (76%)	16/21 (76%)	16/19 (84%)	11/17 (65%)					180/212 (85%)
28	20/28 (71%)	22/28 (79%)	25/27 (93%)	23/25 (92%)	20/23 (87%)	20/23 (87%)	19/22 (86%)	19/22 (86%)	13/20 (65%)						181/218 (83%)
29+	4/5 (80%)	4/5 (80%)	4/5 (80%)	3/5 (60%)	5/5 (100%)	5/5 (80%)	4/4 (100%)	3/3 (100%)							32/37 (86%)
Total	75/102 (74%)	86/100 (86%)	78/97 (80%)	76/93 (82%)	79/89 (89%)	79/87 (91%)	67/83 (81%)	68/80 (85%)	57/70 (81%)	37/47 (79%)	27/29 (93%)	16/20 80%)	9/10 (90%)	1/1 (100%)	755/908 (83%)

Expected number of recordings was calculated using the assumption of 2 recordings in the first week and 1 recording each week thereafter until 36 weeks PMA. As the protocol allowed 4 – 10 days between weekly recordings, this estimate may not be in agreement with the reported protocol deviations.

Table 3

Protocol deviations and adverse events

Event	n (%)
Deviations	**N=96**
aEEG recording not performed according to schedule	76 (79%)
Inaccessible	*19 (25%)*
Too ill	*28 (37%)*
Equipment malfunction	*9 (12%)*
Research personnel not available	*5 (7%)*
Unable to obtain acceptable impedance	*2 (3%)*
Other	*13 (17%)*
Incomplete recording performed (<6 hours)	18 (19%)
aEEG data lost prior to transfer	1 (1%)
Other	1 (1%)
Adverse events	**N=6***
Skin breakdown (all self-resolved)	3
Skin infection of scalp/head at electrode site	0
Medical device event	0
Other event possibly related to aEEG	3
Cold Stress	*1*
Desaturation≠	*1*
Other (inadvertent hair removal by aEEG sensor)	*1*

*Number of infants experiencing adverse events and number of reported events were the same

≠Desaturation event deemed not likely attributable to study intervention