Assessing the Feasibility of Providing a Real-Time Response to Seizures Detected With Continuous Long-Term Neonatal Electroencephalography Monitoring

Cynthia Sharpe,* Suzanne L Davis,* Gail E. Reiner,† Lilly I Lee,‡ Jeff J Gold,† Mark Nespeca,† Sonya G Wang,† Priscilla Joe,§ Rachel Kuperman,‖ Marissa Gardner,‖ Jose Honold,¶ Brian Lane,¶ Ellen Knodel,# Deborah Rowe,** Malcolm R. Battin,†† Renee Bridge,‡‡ Jim Goodmar,‡‡ Ben Castro,‡‡ Maynard Rasmussen,§§ Kathy Arnell,‖‖‖ MaryJane Harbert,¶¶ and Richard Haas##

*Paediatric Neurology, Auckland District Health Board, Auckland, New Zealand; †Department of Neurosciences, Rady Children's Hospital San Diego, University of California, San Diego, California; ‡Department of Neurosciences, University of California, San Diego, California; Departments of §Neonatology and ‖Pediatric Neurology, UCSF Benioff Children's Hospital, San Francisco, California; ¶Department of Pediatrics, Rady Children Hospital San Diego, University of California, San Diego, California; #Division of Neonatology, Rady Children's Hospital, San Diego, California; **School of Nursing, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand; ††Neonatology, Auckland District Health Board, Auckland, New Zealand; ‡‡Division of Neonatology, Department of Pediatrics, University of California, San Diego, California; §§San Diego Neonatology Inc, Sharp Mary Birch Hospital for Women and Newborns, San Diego, California; ‖‖‖Neonatal Research Institute, Sharp Mary Birch Hospital for Women and Newborns, San Diego, California; ¶¶Department of Neurosciences, Sharp Mary Birch Hospital for Women and Newborns, University of California, San Diego; and ##Departments of Pediatrics and Neurosciences, Rady Children's Hospital San Diego, University of California, San Diego, California.

Purpose: Continuous video electroencephalography (cEEG) monitoring is the recommended gold standard of care for at-risk neonates but is not available in many Neonatal Intensive Care Units (NICUs). To conduct a randomized treatment trial of levetiracetam for the first-line treatment of neonatal seizures (the NEOLEV2 trial), we developed a monitoring infrastructure at five NICUs, implementing recent technological advancements to provide continuous video EEG monitoring and real-time response to seizure detection. Here, we report on the feasibility of providing this level of care.

Methods: Twenty-five key informant interviews were conducted with study neurologists, neonatologists, coordinators, and EEG technicians from the commercial EEG monitoring company Corticare. A general inductive approach was used to analyze these qualitative data.

Results: A robust infrastructure for continuous video EEG monitoring, remote review, and real-time seizure detection was established at all sites. At the time of this survey, 260 babies had been recruited and monitored for 2 to 6 days. The EEG technician review by the commercial EEG monitoring company

was reassuring to families and neonatologists and led to earlier detection of seizures but did not reduce work load for neurologists. Neurologists found the automated neonatal seizure detector algorithm provided by the EEG software company Persyst useful, but the accuracy of the algorithm was not such that it could be used without review by human expert. Placement of EEG electrodes to initiate monitoring, especially after hours, remains problematic.

Conclusions: Technological advancements have made it possible to provide at-risk neonates with continuous video EEG monitoring, real-time detection of and response to seizures. However, this standard of care remains unfeasible in usual clinical practice. Chief obstacles remain starting a recording and resourcing the real-time specialist review of suspect seizures.

Key Words: Neonatal seizures, Intensive care unit EEG monitoring, Seizure detection, Neonatal electroencephalography, Critical care pathway.

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Better treatments for neonatal seizures are urgently needed.[1] Efforts to develop better treatments are hindered by the need for systematic continuous video electroencephalography (cEEG) monitoring in any drug trial. Continuous video EEG is the recommended gold standard of care[2] but is not available in many NICUs because of resource constraints.

To conduct the NEOLEV2 trial (NCT01720667), we developed an infrastructure for neonatal cEEG monitoring at five hospitals, using remote review of cEEG monitoring, a commercial EEG monitoring company (Corticare), and automated neonatal seizure detection software to assist in early seizure detection. The five participating hospitals were Rady Children's Hospital of San Diego, Sharp Mary Birch Hospital for Women and Newborns, San Diego, UC San Diego Medical Center, Hillcrest, UCSF Benioff Children's Hospital in Oakland, and Auckland Hospital in Auckland, New Zealand. At the time

of this study, 260 neonates had undergone cEEG monitoring for periods of 2 to 6 days. Longer periods of monitoring were required for neonates with hypoxic ischemic encephalopathy undergoing 72 hours of hypothermia and an additional subsequent rewarming period.

Recent research demonstrates that early detection and treatment of seizures lead to better response to treatment.[3] In addition, we know that an increased seizure burden is associated with worse neurological outcome.[4–6] The same infrastructure for early seizure detection and treatment is therefore desirable for standard clinical care, outside of a research protocol.

To assess the feasibility of providing this level of care in usual clinical practice, we report here on the challenges encountered during the NEOLEV2 study related to monitoring. We report the findings of key informant interviews conducted with study neonatologists, neurologists, Neuro-intensive care nursery (NICN) nurses, coordinators, and EEG technicians from the commercial EEG monitoring company.

Recordings were made on study-dedicated Cadwell EEG machines that displayed three-channel amplitude-integrated EEG trends, video, and full-montage raw EEG at the bedside. (A 10–20 International placement montage modified for neonates was used recording from 10 scalp electrodees at FP1, FP2, FZ, C3, CZ,C4, T3, T4, O1 and O2.)

Most EEG recordings were started after hours. Where EEG technicians were not available, monitoring was started by respiratory therapists and neonatal intensive care unit nurses with special training in the care of infants with neurological problems (NICN nurses) using the Jordan elasticated EEG lead placement device.

The automated neonatal seizure detector algorithm ran on all acquisition stations during recording.[7–9]

In the first 24 to 48 hours, EEG was continuously reviewed through the internet using TeamViewer software by EEG technicians from the commercial EEG monitoring company. Study neurologists at each site reviewed the record regularly and whenever contacted by the commercial EEG monitoring company for suspected seizure. From October 2015, the automated neonatal seizure detector algorithm was systematically used in real-time review as a research tool to aid seizure detection. Direct email alert generated by the seizure detector algorithm was available to study neurologists if they chose to use this function. All treatment decisions were made by study neurologists who could also access and review the live EEG remotely through the internet (Fig. 1).

METHODS

Key informant interviews were conducted by phone with research team members at all study sites. Study neurologists (9), study neonatologists (11), site principal investigators, site coordinators, research nurses, and a respiratory therapist were interviewed.
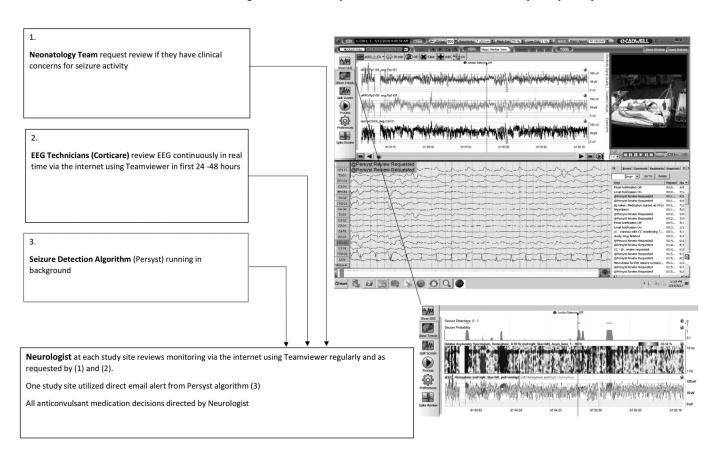

FIG. 1. Electroencephalography monitoring system used for the NEOLEV2 study.

Electroencephalography technicians from the commercial EEG monitoring company (6) who had monitored frequently for the study completed a written questionnaire sent by email.

Questions were developed, and phone interviews were conducted by the first author (C.S.), a neurologist and site principal investigator for the study. Questions are included as **Supplemental Digital Content 1**, (see **appendix**, http://links.lww.com/JCNP/A38). Topics explored included the following:

1. Continuous video EEG monitoring practice before the study
2. Difficulties encountered implementing the NEOLEV2 monitoring strategy
3. Differences between EEG monitoring provided for study patients and patients not in the study
4. Problems encountered related to EEG monitoring during the study
5. Impressions of the commercial EEG monitoring company Corticare
6. Impressions of the automated neonatal seizure detection algorithm provided by the EEG software company Persyst
7. The feasibility of offering a real-time response to cEEG monitoring for all at-risk neonates and suggestions as to how this could be improved
8. Who should be responsible for interpretation of cEEG in the NICU
9. Level of interest in training in the interpretation of neonatal EEG

Field notes were made during each interview and summarized. A general inductive approach was used to analyze this qualitative data. Summarized results were sent back to research team members who had been interviewed, and feedback was invited.

RESULTS

Technical Problems Encountered

An infrastructure and practice for remote review of cEEG was operational at two of five sites before commencing the study and had to be developed at the other sites. In four hospitals, internet connectivity was initially restricted to a subset of NICU bed spaces, necessitating disruptive moves of critically sick infants to conduct remote EEG review. Over the course of the study, all five sites developed the capacity to monitor from all bed spaces. Three of five sites used Ethernet and the hospital server system as the conduit for remote review by the end of the study. One site now uses a 4G wireless conduit to the hospital server. At the fifth site where a hospital wireless network was the only available access for this research, internet speeds were marginal for high-speed review, and review was compromised by frequent disconnection problems.

During the period that the study was conducted, clinical practice evolved so that long-term cEEG became routine at four of five sites outside the study. At the fifth site, Brainz monitoring (four lead amplitude-integrated EEG with raw trace EEG without video reviewed by neonatologists) remains the standard of clinical care outside the study.

The Cadwell EEG machines, Easy III and Persyst software, and TeamViewer review system generally proved robust and secure for EEG acquisition, display, and remote review.

On one occasion monitoring was interrupted briefly when TeamViewer shut down their software globally to patch a software vulnerability. Early difficulties were encountered with incompatibility of versions of TeamViewer between acquisition and reader stations.

Infrequently, disruptions in monitoring were caused by EEG machine problems. Such problems were usually fixed by a simple reboot and restart. On two occasions, a Windows software update led to a disconnection of the EEG amplifier. Electroencephalography monitoring was interrupted for days until technical assistance could be obtained to diagnose the problem and reconnect the amplifier. At three sites, monitoring was shut down temporarily when the hard drive for the EEG machine ran out of memory.

Each disruption in monitoring was considerably problematic. Once a new clinical service is offered, even on a research basis, any disruption in the smooth running of that service quickly becomes unacceptable.

Starting a Recording

Networks of NICN nurses or respiratory therapists were available to start an EEG recording after hours at three sites before the commencement of the study. These networks became stronger during the study, limiting the potential delays caused by needing to call an EEG technician to start a recording after hours. At one study site, the site principal investigator applied leads and started recordings for 18 months before transferring this duty to a study nurse. Efforts are ongoing to train a group of nurses in this skill set. At the fifth site, there remains no capability for full-montage EEG monitoring after hours, limiting recruitment to the study. At that site, Brainz monitors are applied after hours, until EEG technicians are available to start a full-montage video EEG recording.

At all sites, the process of starting an EEG recording remains a significant resource commitment. NICN nurses and respiratory therapists estimate that it takes 30 minutes to an hour for an experienced technician to start a recording. Furthermore, at least some leads will need to be reapplied or fixed every 4 hours on average. Reapplication was required less frequently at one site where needle electrodes are used.

Having circumvented involvement of EEG technicians in starting an EEG recording, we inadvertently relinquished their technical support for problem shooting software and equipment failures and archiving of EEG recordings. Electroencephalography technicians were involved in the archiving of the research EEGs at only two study sites and in maintaining the electrodes during working hours at three study sites. Elsewhere, nurses maintained the electrodes throughout the monitoring period, and site principal investigators assumed responsibility for archiving EEG records. NICN nurses who have taken on the responsibility of starting the recording reported frustration at expectations that they would be able to solve technical issues, when these are well outside their brief.

Utility of Real-Time Remote Review by Electroencephalography Technicians From the Commercial Electroencephalography Monitoring Company Corticare

All neonatologists surveyed ($n = 11$) felt that the commercial EEG monitoring company added value and a layer of

security for the patient. Study staff reported that having an EEG technician reviewing the EEG continuously was reassuring and attractive to families and helped with recruitment to the research study.

Eight of nine neurologists reported personal experience of monitoring by the commercial EEG monitoring company leading to earlier detection of seizures, especially overnight.

Neurologists reported that they tended to check the record less often if they knew the commercial EEG monitoring company was monitoring, which reduced their work load. Conversely, being called for technical issues or for false-positive seizure detections increased demands on their time. Overall, four of nine study neurologists felt that having the commercial EEG monitoring company monitoring a study patient reduced their own work in monitoring. Four neurologists felt their overall work load was unchanged. One neurologist felt having the involvement of the commercial EEG monitoring company increased his work load in monitoring. Four neurologists spontaneously commented that performance of the commercial EEG monitoring company was generally positive but very operator-dependent; most technicians were proficient, but some were less familiar with neonatal EEG.

Errors in communication occurred when monitoring technicians typed information onto the computer screen, which should have been reported by phone call to study personnel. A technician unfamiliar with NICU monitoring on one occasion instructed NICU staff not to touch the neonate undergoing monitoring as this was generating artifact. The commercial EEG monitoring company was very responsive to all feedback, and communication became more streamlined as the study progressed.

Technicians from the commercial EEG monitoring company themselves, when surveyed about their work on the NEOLEV2 study, reported difficulties when reviewing remotely trying to read EEG that was contaminated with artifact from loose electrodes and being unable to remedy this artifact. Technicians also reported frustration with poor camera image because of lighting or camera placement. Technicians from the commercial EEG monitoring company were unable to monitor study subjects when the EEG was being reviewed by other study personnel. The technicians dealt patiently with repeated internet disconnection problems with one study site, where at times, reconnection was required every 15 minutes and sometimes more frequently. Technicians also reported it was difficult contacting a patient's bedside nurse with the anonymized data set given to them, an issue that would only occur within a research setting.

Utility of the Automated Neonatal Seizure Detector Algorithm Provided by the Persyst Electroencephalography Software Company

All study neurologists found the automated neonatal seizure detector algorithm, a useful tool for seizure detection. Many commented that the algorithm demonstrated fairly high sensitivity but that false positives (e.g., from patting artifact) were common. The accuracy of the algorithm was not such that it could be relied on or used without review by an electroencephalographer. An instant messaging alert function was used by only two of nine study neurologists, others finding disruption from false-positive alerts too disruptive to other work commitments and sleep.

Resources for Real-Time Interpretation

Study neurologists were asked if they considered it feasible as they were currently resourced to provide real-time review and response to cEEG for at-risk neonates outside of the research study and as part of routine clinical care.

None felt that they were adequately resourced to provide this, and several stated that they were already under-resourced clinically.

It should be emphasized that, at four of the five sites, a clinical practice of cEEG monitoring for all at-risk neonates has evolved in recent years that is not dissimilar to what was provided within the NEOLEV2 study. Electroencephalography monitoring was usually reviewed at least 12 hourly at all sites, increasing, for seizing or very high-risk subject to as frequently as every hour during the day. Review of the EEG overnight remains infrequent at all sites. At the hospitals with the best resources, this constituted the main difference between monitoring as it happened within the research study and how it is provided for all at-risk neonates.

Solutions Suggested by Study Neurologists and Neonatologists Which Could Increase the Clinical Feasibility of a Real-Time Response to Neonatal Seizure Detection

Study neurologist and neonatologists were asked what could improve the feasibility of a real-time response to neonatal seizure detection. Suggestions included better automated seizure detection and a larger contingent of electroencephalographers. It was considered that a separated on-call roster would be required, such that the neurologist on duty to review and respond to neonatal (and other) EEG monitoring was not also on duty for general pediatric neurology, for neurologists to sustain this level of care.

Better training of EEG technicians and access to in-hospital EEG technicians who could both review studies and troubleshoot leads and equipment was suggested.

All neurologists were supportive of the idea that EEG technicians, neonatologists, and/or NICN nurses with the appropriate comprehensive training and oversight by a neurophysiologist might be appropriate first-line personnel for neonatal cEEG review.

Most surveyed neonatologists, NICN nurses, and EEG technicians expressed interest in obtaining comprehensive training and certification in neonatal seizure detection.

DISCUSSION

There have been multiple recent technological advances in cEEG monitoring. These include smaller more affordable video EEG machines, improved internet speed and security, software advances for remote review and for automated seizure detection, and lead placement devices to assist non-EEG technicians in starting EEG acquisition. Continuous EEG review by EEG technicians is a commercially available service. As we embarked on the NEOLEV2 study, we felt optimistic that these advances meant that we would be able to demonstrate within our study that it was now feasible to provide the gold standard of cEEG monitoring for all at-risk neonates with rapid detection and a real-time response to seizures. Although our experience has

demonstrated that this is now technically feasible, the surveyed responses from our dedicated study personnel show that it is still not practical to provide this level of care clinically for all at-risk neonates in most NICUs.

The two most significant factors limiting the provision of this level of care were the difficulties surrounding the starting of a recording after hours and resourcing the physician review of suspect seizures in real time after hours. In addition, although continuous EEG review by EEG technicians is available, it is not funded in most hospitals. These factors are part of a much greater problem of insufficient resources for NICU cEEG monitoring in general.

It has been recognized for some time that because neonatal seizures are so frequently entirely subclinical, cEEG monitoring of at-risk neonates is required for their reliable detection.[10–13] The more recent dramatic upsurge in clinical demand for NICU cEEG monitoring reflects the increasing evidence that neonatal seizures are damaging.[4,14–17] Although a causal link between seizures and brain injury in human subjects has not been proven, it is reasonable to hope that early detection and treatment of seizures may reduce brain injury. Long-term neurodevelopmental outcomes after neonatal seizures are poor.[18–20] Preventing permanent neurodevelopmental disability in even a small percentage of these children would not only improve quality of life for these children and their families but would greatly reduce the health care costs associated with caring for a child with permanent neurodevelopmental disability. The dramatic increase in the amount of neonatal cEEG monitoring performed in many hospitals has often occurred without the increased resource required to sustain it. Similar resource issues have been faced by adult and pediatric ICUs charged with the provision of cEEG monitoring for their patients.[21–24] Ability to respond to the new demand for ICU cEEG monitoring is hindered by a reimbursement system that only partly compensates for the increased costs associated with acquiring, reviewing, and responding to ICU cEEG monitoring as compared with non-ICU video EEG monitoring.[23] Non-ICU cEEG monitoring, for example, cEEG for epilepsy diagnosis or epilepsy surgery assessment, can be set up during working hours and in many cases can be reviewed electively and less frequently by interpreting neurophysiologists.

Solutions to these funding and resource issues are urgently required if we are to sustainably provide the gold standard of care with cEEG monitoring for at-risk neonates, and through early detection and treatment of seizures improve their neurodevelopmental outcomes.

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