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EEG Monitoring during Therapeutic Hypothermia in Neonates, Children, and Adults

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Abstract

Therapeutic hypothermia is being utilized as a neuro-protective strategy in neonates, children, and adults. The most common indications are hypoxic ischemic encephalopathy in neonates and post cardiac arrest in adults. Electroencephalographic monitoring use is increasing in critical care units, and is sometimes a component of therapeutic hypothermia clinical pathways. Monitoring may detect non-convulsive seizures or non-convulsive status epilepticus, and it may provide prognostic information. We review data regarding indications for therapeutic hypothermia and electroencephalographic monitoring in neonatal, pediatric, and adult critical care units, and discuss technical aspects related to such monitoring.

Keywords

Cardiac arrest; EEG; neonatal hypoxic ischemic encephalopathy; non-convulsive seizures; seizures; therapeutic hypothermia; traumatic brain injury

INTRODUCTION

Therapeutic hypothermia (TH) is known to mitigate brain injury in a variety of animal models and is associated with improved outcome after neonatal hypoxic ischemic encephalopathy (HIE) and adult cardiac arrest. While efficacy data are not available in the non-neonatal pediatric group, implementation of TH is feasible in pediatric settings and it is sometimes utilized based on adult and neonatal data. Although research continues regarding optimal TH methodology, it is now often utilized after cardiac arrest in adults, hypoxic ischemic brain injury in neonates, and sometimes after cardiac arrest in children.

Seizures are known to occur during TH across all age groups. Often there is no corresponding clinical correlate, and thus these seizures are referred to as electrographic-only seizures or non-convulsive seizures (NCS). This may be due to either physiologic electromechanical uncoupling or pharmacologic paralysis. It remains unclear whether these acute symptomatic seizures are biomarkers of brain injury or whether they independently impact outcome. In a variety of settings, NCS have been associated with worse outcome, and mechanisms by which NCS might lead to worse outcome have been demonstrated. These include alterations in intracranial pressure, induction of metabolic crisis, and alterations in cerebral perfusion. Thus, some centers perform EEG monitoring during TH to detect NCS. Additionally, EEG features may provide objective data to guide prognostication.

This review addresses the use of TH in the neonatal, pediatric, and adult populations, summarizes the data regarding EEG monitoring in each population, and discusses technical issues involved in performing EEG monitoring in an intensive care unit setting.

NEONATES

Indications and Implementation of Therapeutic Hypothermia

Since the publication of the first two large randomized clinical trials on TH for near-term and term newborns in 2005 (Shankaran et al. 2005, Gluckman et al. 2005) moderate TH is fast becoming a standard of care in NICUs for neonatal encephalopathy (NE) as a result of hypoxic ischemic encephalopathy (HIE) or birth asphyxia. HIE occurs in 1 to 2 per 1000 term live births and is a major cause of death and disability in newborns (Vannucci 1990, Lawn et al. 2005). Over 13 clinical studies including five prospective randomized trials have shown that moderate TH (core temperature of 33 to 34°C) reduces mortality and/or moderate-severe neurodevelopmental disability (Shah 2010) in newborns (≥ 36 weeks gestation) cooled within six hours life.

Unlike in pediatric or adult hypothermia, there are two methods of neonatal cooling: whole-body (cooling blanket) or head (cooling cap) cooling (Shankaran et al. 2005, Gluckman et al. 2005). Both methods cool to a core temperature (esophageal or rectal) of 33 to 34°C, typically regulated by servo-control. Infants are cooled for 72 hrs and gradually rewarmed by 0.5 degree/hour or over 24 hours.

Newborns with NE due to HIE are identified based on: 1) physiologic indicators of acidosis (cord blood gases pH ≤ 7.0 or base deficit ≥ 16) or clinical history of a major perinatal event (i.e., uterine rupture, placental abruption, maternal trauma) in the setting of persistently low Apgar scores and 2) neurologic examination findings of moderate-severe NE or seizures. Selective-head cooling protocols have typically included amplitude-integrated EEG (aEEG, a trend analysis of either 1 to 2 channels of EEG; see below) to assess for moderate or severe encephalopathy. Neonatal TH protocols have evolved to allow for earlier cooling using ice packs in transport (Jacobs 2011) and studies are currently underway to evaluate the effectiveness of cooling infants with more mild HIE, late preterm infants (32 to 36 weeks gestational age), and delayed cooling (≥ 6 hours of life).

EEG Monitoring during Neonatal Therapeutic Hypothermia

EEG remains the gold standard for assessing encephalopathy and detecting seizures in neonates. Grading encephalopathy in a newborn by physical exam can be difficult and subjective (Holmes et al. 1982). Seizures, both clinical and non-convulsive, are common in newborns with HIE (Laroia et al. 1998, Mizrahi and Kellaway 1987, Nash et al. 2011, Wusthoff et al. 2011) and can be associated with worse prognosis (McBride et al. 2000, Pisani et al. 2008, Legido et al. 1991). The addition of anticonvulsant agents like

phenobarbital can cause electroclinical dissociation (no clinical seizures but ongoing electrographic seizures), thereby making it difficult to determine the success of therapeutic interventions without EEG monitoring (Scher et al. 2003, Connell et al. 1989).

Protocols for neuromonitoring during cooling vary depending on each center's resources and personnel, and there are no established guidelines. EEG monitoring was not required in any of the neonatal cooling trials. Recent surveys indicate that most NICUs have access to EEG and aEEG, with EEG typically interpreted by neurophysiologists and aEEG typically interpreted by neonatologists (Boylan et al. 2010, Filan et al. 2007).

The ideal time for EEG monitoring depends on the purpose of the evaluation. If the EEG is being used to assess the degree of brain injury (encephalopathy), pre-hypothermia literature suggests that EEG findings after 24 hours of insult/life and before one week of insult/life have the highest sensitivity and specificity (Tharp 1997, Pezzani et al. 1986, Monod et al. 1972). The ability to provide a neurologic prognosis is further enhanced by obtaining EEGs at multiple time points (Monod et al. 1972, Sarnat and Sarnat 1976, Takeuchi and Watanabe 1989). If continuous EEG monitoring (cEEG) is not performed, serial routine EEGs, such as an initial recording, after rewarming, and at 1 to 2 weeks of life can provide an initial assessment of encephalopathy and determine the patient's trend towards recovery or worsening (Sarnat and Sarnat 1976, Takeuchi and Watanabe 1989, Holmes and Lombroso 1993). If the EEG is being used to detect seizures in the setting of HIE, then a routine EEG recording within 12 to 36 hours of insult/life and during rewarming may capture some seizures (Laroia et al. 1998, Nash et al. 2011, Wusthoff et al. 2011, Clancy et al. 2005). cEEG monitoring is ideal for precise detection of seizures since seizures may occur outside that time window (Wusthoff et al. 2011) and many seizures are non-convulsive (Nash et al. 2011, Wusthoff et al. 2011) especially after treating with an anticonvulsant (Scher et al. 2003, Connell et al. 1989). Studies are ongoing to determine the utility and appropriate timing of EEG monitoring during TH.

Many NICUs with limited access to EEG have obtained aEEG devices (Brainz Instruments, Auckland, New Zealand; Olympic Medical, Seattle, WA, USA). aEEG is a trend generated from single channel (P3, P4) or two channel (C3-P3, C4-P4) EEG recordings that are typically filtered to exclude frequencies other than 2 to 15 Hz and then displayed on a compressed time scale of six centimeters per hour, so that six hours of EEG activity are viewed per page (Hellström-Westas et al. 2008, El-Dib et al. 2009). Visual patterns or amplitude criteria allow the reviewer to assess the severity of encephalopathy as well as to monitor for seizures (al Naqeeb et al. 1999, Hellström-Westas et al. 2006, Spitzmiller et al. 2007). Depending upon the number of electrodes used and location, aEEG can detect 46 to 76% of the seizures identified by conventional full-array EEG (Shellhaas et al. 2007, Wusthoff et al. 2009, Rennie et al. 2004, Toet et al. 2002, Hellström-Westas 1992). Two channel aEEG with the ability to review the raw EEG tracing has the highest sensitivity (Shah et al. 2008). It has been recommended that seizures identified on aEEG be verified with a standard EEG recording. Those NICUs with access to EEG may adopt a protocol for serial routine EEGs or ideally be able to continuously monitor their infants during TH and rewarming. Since many EEG recording systems have the capability to display trends such as aEEG, it can be useful to display the aEEG trend on the bedside recording machine for the neonatologist to have a continuous trend to review at the bedside for seizures and significant changes in background. The neurophysiologist can also utilize aEEG to quickly focus on areas of interest such as potential seizures, resolution of seizures, or increasing discontinuity or suppression of the background.

PEDIATRIC

Indications and Implementation of Therapeutic Hypothermia

Cardiac Arrest—Pediatric cardiac arrest occurs in more than 8,000 children per year in the United States. Survival rates range from 5 to 27% and half of surviving children have long-term physical, psychological, social, financial, and quality of life burdens (Nadkarni et al. 2003, Atkins et al. 2009). In the 1970s and 1980s following near drowning, TH, in conjunction with pentobarbital, was used to improve neurologic outcome (Conn et al. 1978). Unfortunately, further evaluation of these therapies in the mid 1980s showed that these combined therapies were not associated with improvement in outcome and TH use was largely discontinued (Bohn et al. 1986). Recently, given data that TH improves outcome after adult cardiac arrest and neonatal HIE, there is renewed interest in TH after pediatric cardiac arrest. However, to date there have been no published prospective trials evaluating efficacy.

Two recent retrospective studies compared induced TH and normothermia in children successfully resuscitated from pediatric cardiac arrest (Fink et al. 2009, Doherty et al. 2009). Both showed that there was no benefit to treating patients with therapeutic hypothermia once controlling for potential confounders. Doherty et al. (2009) performed a multicenter retrospective cohort study across five centers, of which only three utilized hypothermia. 88% of the study population was children with underlying heart disease and 94% of the arrests were in-hospital. There was variability in the temperature to which patients were cooled (33.7 ± 1.3°C) and the duration of hypothermia (20.8 ± 11.9 hours). Despite baseline differences between the hypothermic and normothermia group, there were no was difference in outcome once controlling for multiple variables. Fink et al. (2009) evaluated a single center's retrospective experience with induced TH for primarily asphyxia-associated cardiac arrests. Only 8% of patients had underlying heart disease and only 9% suffered in-hospital cardiac arrests. There was no standard protocol for induction, maintenance, or rewarming. While they observed no significant difference in outcome between the normothermic and hypothermic groups, it was evident that patients treated with TH had suffered more severe injury, as reflected in their longer durations of cardiac arrest and more epinephrine doses required to obtain return of spontaneous circulation (Fink et al. 2009). Both of these studies provide important initial assessments of TH following pediatric cardiac arrest, but are limited by their retrospective approach and lack of explicit protocols.

One study has systematically evaluated the feasibility of a standard algorithm for induction and maintenance of TH following pediatric cardiac arrest using surface cooling (Topjian et al. 2011). Following resuscitation from cardiac arrest children were cooled to 32 to 34°C with a surface device using a standardized protocol. Rectal temperature of ≤ 34°C was achieved in 1.5 hours from cooling initiation. Approximately 80% of the time patients were maintained between 32 to 34°C. Overshoot hypothermia (< 32°C) was observed in 15% of measurements, a finding that was common is an adult study as well (Topjian et al. 2011, Merchant et al. 2006). Other side effects were hypokalemia (67%) and bradycardia (58%). However, there were no episodes of bleeding or ventricular tachyarrhythmia that required treatment. Six of 12 (50%) patients survived to discharge (Topjian et al. 2011).

Despite protocols to induce and maintain TH in children following cardiac arrest, to date, it has not been shown to be an efficacious therapy. Based largely on adult data, the current recommendation from the American Heart Association is that "therapeutic hypothermia (32°C to 34°C) may be considered for children who remain comatose after resuscitation from cardiac arrest" (Kleinman et al. 2010). A multicenter randomized clinical trial (Therapeutic Hypothermia After Pediatric Cardiac Arrest, www.thapca.org) is underway comparing TH (32 to 34°C) to therapeutic normothermia (36 to 37.5°C).

Traumatic Brain Injury—Traumatic brain injury (TBI) is the leading cause of mortality and severe morbidity in children. According to the Centers for Disease Control and Prevention, approximately 475,000 children under the age of 14 sustain traumatic brain injury annually (Langlois et al. 2004). Three early phase clinical trials showed the implementation of TH for pediatric TBI to be feasible (Hutchison et al. 2006) and safe (Adelson et al. 2005, Biswas et al. 2002), but were not powered to detect efficacy. Subsequently, a randomized controlled trial of TH (32 to 33°C) for 24 hours following severe pediatric TBI found hypothermia to be no more effective than normothermia (Hutchison et al. 2008). Subjects were randomly assigned to TH or normothermia within eight hours of brain injury and cooled for 24 hours. There was a trend for higher mortality in the cooled group and there was no difference in neurologic outcomes between the TH and normothermia groups. Subjects in the TH group had more hypotension in the rewarming period (Hutchison et al. 2008). Criticisms of this study are that cooling was started too late, not maintained through the period of peak swelling (approximately 48 hours), and hypotension was not adequately controlled during the rewarming period. Currently, another pediatric randomized controlled trial initiating TH within six hours of injury and treating for 48 hours in underway (www.coolkidstrial.org).

Therapeutic Hypothermia Protocols

The optimal TH management algorithm for children has not been fully defined, but some similarities underlie the algorithms utilized at many institutions. The child is generally stabilized and resuscitated, and then as quickly as possible, if a clinician deems cooling to be appropriate, hypothermia is induced using an external cooling blanket. Two core temperature probes are placed usually in the esophagus, the bladder, or the rectum and one is connected to a cooling machine that controls the temperature of a blanket that is below the patient. The second temperature probe is utilized to verify the temperature measured on the first probe. Hypothermia (32 to 34°C) is maintained usually for 12 to 72 hours depending upon clinician choice. During, induction of TH, clinicians closely monitor for hypokalemia, hypophosphatemia, hyperglycemia, shivering, and diuresis. Rewarming occurs slowly to minimize associated side effects including: hypotension, hyperkalemia, rebound hyperthermia, and possibly cerebral edema.

EEG Monitoring

NCS and non-convulsive status epilepticus (NCSE) often occur in the setting of acute HIE. Retrospective series of acutely ill children with NCS and NCSE have reported HIE as a common acute etiology when NCS are detected (Hyllienmark and Amark 2007, Abend and Dlugos 2007, Tay et al. 2006, Jette et al. 2006). Similarly, a prospective series of children who underwent EEG monitoring due to altered mental status and acute encephalopathy found that 39% of 31 children with acute HIE had NCS (Abend et al. 2011a). However, exact epidemiologic data are not available since not all children with acute HIE underwent cEEG, and these studies included children who did and did not receive TH as a component of their management.

One prospective study enrolled 19 consecutive children with a median age of 11 months undergoing TH after cardiac arrest, all of whom underwent cEEG for a mean duration of 68 hours as part of the clinical TH pathway that involved TH for 24 hours, warming over 12 to 24 hours, and then cEEG during an additional 24 hours of normothermia. Electrographic seizures occurred in 47% (9 of 19). These constituted non-convulsive status epilepticus in 67% (6 of 9) and only had a clinical correlate in 33% (3 of 9). Seizures began during the first half of hypothermia in one, the second half of hypothermia in four, and during re-warming in four patients (Abend et al. 2009). While prospective enrollment may have avoided some of the confounding problems inherent in retrospective studies, these children

were all considered to have experienced sufficient acute injury to warrant management with TH, and thus may represent a more severely injured group than all children with HIE. Seizures occurred in all eight patients with a severely abnormal background (positive predictive value = 100%) and in only one patient with a mildly/moderately abnormal background. Background assessment was made in the first 30 minutes of the EEG tracing, and severe background abnormalities included excessive discontinuity, burst suppression, or highly attenuated-featureless tracings (Abend et al. 2009). If these data are generalized, then initial EEG findings might help direct limited cEEG resources to children at higher risk for seizures. Further study is needed to determine whether detecting and managing NCS improves outcome.

Beyond NCS detection and management, EEG data may provide useful prognostic information after acute HIE. While individual clinical, laboratory, imaging, and neurophysiologic features may be useful in outcome prediction, none has perfect predictive value (Abend and Licht 2008). Utilization of EEG is appealing since it can be performed non-invasively at the bedside and provides objective data. Unfortunately, an important limitation of EEG-based prognosis is the unclear reproducibility of EEG interpretation in critically ill patients (Abend et al. 2011b, Husain 2006, Gerber et al. 2008, Hirsch et al. 2005, Ronner et al. 2009). However, some EEG features such as continuity do have high inter-rater agreement in critically ill children with acute HIE (Abend et al. 2011b) and EEG classification systems that group EEG features into predictive categories have been developed (Nishisaki et al. 2007, Kessler et al. 2011).

Some EEG background features are known to have prognostic significance in children when TH is not utilized (Nishisaki et al. 2007, Pampiglione and Harden 1968, Tasker et al. 1988, Cheliout-Heraut et al. 1991, Ramachandrannair et al. 2005, Mandel et al. 2002, Pampiglione et al. 1978, Evans and Bartlett 1995). Patients with more severely abnormal EEG backgrounds tend to have a worse short-term outcome than patients with only mild/moderate background abnormalities. Pediatric studies have reported that burst suppression (Pampiglione and Harden 1968), excessive discontinuity (Mandel et al. 2002), severe attenuation (Tasker et al. 1988), lack of reactivity (Ramachandrannair et al. 2005, Mandel et al. 2002), and generalized epileptiform discharges (Mandel et al. 2002) are associated with unfavorable prognosis. Conversely, rapid EEG improvement (Pampiglione et al. 1978), reactivity (Cheliout-Heraut et al. 1991), and normal sleep patterns (Cheliout-Heraut et al. 1991, Evans and Bartlett 1995) are associated with good prognosis. A retrospective study of 34 children resuscitated from cardiac arrest who had EEGs performed during the initial seven days after cardiac arrest reported that a more severely abnormal EEG score was associated with poor neurologic outcome. The positive predictive value of electroencephalography grade 4 to 5 for poor neurologic outcome was 90%, and negative predictive value of EEG grade 1 to 2 for poor neurologic outcome was 91%. The EEG grades were: 1) continuous, not low voltage, not slow, 2) continuous, low voltage or slow, 3) continuous, low voltage, and slow, 4) discontinuous, and 5) isoelectric (Nishisaki et al. 2007). Knowledge of clinical status is essential to ensure that EEG changes are not pharmacologically induced or compromised by scalp edema or extra-axial fluid collections.

Less data are available regarding the prognostic significance of EEG features when TH is utilized and it is unclear whether the EEG features that predicted outcome prior to utilization of TH retain their predictive value when TH is utilized. At extremely low temperature the EEG may develop a discontinuous and then isoelectric pattern (Levy 1984, Stecker et al. 2001, Rodichok et al. 1994) but these severe EEG abnormalities are not seen with the moderate hypothermia temperatures used for TH in adults (Stecker et al. 2001, Kochs 1995) or neonates (Horan et al. 2007). EEG patterns evolve during the course of TH (Abend et al. 2009, Kessler et al. 2001), but it remains unknown whether this evolution results from

evolving brain injury, temperature modulation, sedative medication adjustments, or all three. In children undergoing deep hypothermia during cardiac surgery, slowing and then attenuation occurred during the procedure but by the end of the procedure activity returned to normal in most children (Rodichok et al. 1994), suggesting hypothermia does not have a persisting impact on EEG features in most children once they return to normothermia. One study enrolled 35 children after cardiac arrest managed with a standard clinical TH algorithm. Thirty minute EEG segments obtained during TH and during the first 30 minutes of normothermia were scored in a standardized manner and categorized by three pediatric electroencephalographers. Three EEG categories were used: 1) continuous and reactive tracings, 2) continuous but unreactive tracings, and 3) any degree of discontinuity, burst suppression, or lack of cerebral activity. The primary outcome was unfavorable short-term outcome defined as Pediatric Cerebral Performance Category score of 4 to 6 (severe disability, vegetative, death) at hospital discharge. For tracings obtained during hypothermia, patients with EEGs in categories 2 or 3 were far more likely to have poor outcome than those in category 1. Similarly, for tracings obtained during normothermia, patients with EEGs in categories 2 or 3 were far more likely to have poor outcomes than those in category 1. These data suggest even when TH is utilized, lack of reactivity and discontinuity is associated with unfavorable outcome. However, these features did not have 100% predictive value, and thus cannot be used in isolation to make decisions related to withdrawal of technological support (Kessler et al. 2011).

ADULTS

Indications and Implementation of Therapeutic Hypothermia

Many diseases associated with severe intracranial hypertension, and less so with cerebral ischemia, have been considered or tested as targets for mild (32 to 35°C) or moderate (28 to 32°C) TH. The first clinical trial using TH was in severe TBI and showed mild TH was not associated with clinically significant medical complications (Clifton et al. 1993). Clinical trials in cardiac arrest, severe TBI, stroke, acute hepatic failure, and a variety of other acute neurologic diseases have occurred subsequently.

Cardiac Arrest—After successful resuscitation from cardiac arrest, most adults are comatose. Approximately 70% of these patients die while hospitalized (Nolan and Laver 2007) and more than one-third of survivors are left with neurologic deficits (Longstreth et al. 1983). TH is most commonly used for cardiac arrest. One multi-center randomized study demonstrated that in adults resuscitated from cardiac arrest to ventricular fibrillation, TH was associated with an increased rate of favorable neurologic outcome (55% of 136 with TH versus 39% of 137 with normothermia) and reduced mortality at six months (41% with TH versus 55% with normothermia) (Hypothermia after Cardiac Arrest Study Group 2002). A second multi-center randomized study demonstrated more patients treated with hypothermia had a good outcome defined as discharge home or to rehabilitation facility (49% of 43 with TH versus 26% of 34 with normothermia). Even after adjusting for age and time to return of spontaneous circulation, the odds ratio for good outcome was 5.25 for TH as compared to normothermia (Bernard et al. 2002). A subsequent meta-analysis of four randomized studies found that mild TH within six hours of ventricular fibrillation or pulseless ventricular tachycardia arrest reduced mortality by 20% and decreased incidence of poor neurological outcome by 27% (Cheung et al. 2006). Treatment with mild induced TH in unconscious adults after out-of-hospital ventricular fibrillation or pulseless ventricular tachycardia cardiac arrest is recommended by the American Heart Association (Nolan et al. 2003) and is now considered standard of care. Centers are experimenting with TH for expanded cardiac arrest populations including those whose initial rhythm is pulseless electrical activity or asystole, and those with in-hospital cardiac arrest.

Traumatic Brain Injury (TBI)—Investigations done in the 1950s to 1960s showed that brain swelling and intracranial hypertension were significant problems in severe TBI. Virtually all subsequent clinical trials of more than 1000 patients examining TH's effect on intracranial pressure in severe TBI (Glasgow Coma Scale < 9) have shown it to decrease intracranial pressure. However, its effect on clinical outcome has been mixed (Marion and Bullock 2009). Several single-center trials showed a benefit in functional outcome 6 to 24 months after severe TBI, but two large multi-center trials enrolling a total of 483 patients did not show benefit. In the multi-center studies, inhomogeneity in patient management strategies across centers (e.g., use of barbiturate medications and hemodynamic management) may explain why their studies were discrepant from the majority of single-center studies. A recent meta-analysis of six clinical trials included 694 patients and demonstrated that TH was associated with a non-significant reduction in mortality and a significant improvement in functional outcome (Bratton et al. 2007). TH has also been shown to be beneficial when added to other interventions for TBI such as hemicraniectomy (Qiu et al. 2007). Current guidelines support the use of TH by experienced clinicians for refractory intracranial hypertension as one of several available medical options (Marion and Bullock 2009). Multiple additional clinical trials are currently in progress. Given the relatively high prevalence of NCS after moderate-severe TBI (Vespa 2005, Claassen et al. 2004), it is reasonable to perform cEEG in this group of patients if resources permit.

Stroke—Clinical benefit of TH in acute ischemic stroke has not yet been investigated in large randomized controlled trials. Feasibility of TH but no functional or mortality benefit has been demonstrated in early phase studies with 50 or fewer patients per study in ischemic stroke, hemispheric stroke, and hemispheric stroke with hemicraniectomy. Decreased edema in large stroke occurred with TH, but problems with rebound intracranial hypertension during rewarming were present (De Georgia et al. 2004, Schwab et al. 2001, Els et al. 2006). Clinical protocols must be further improved before TH undergoes large-scale clinical trials for ischemic stroke. There are relatively fewer studies of TH for other types of stroke, such as poor-grade subarachnoid hemorrhage and spontaneous intracerebral hemorrhage (Gasser et al. 2003, Feng et al. 2002).

Acute Hepatic Failure—Approximately 20% of patients with acute hepatic failure, defined as abrupt onset of hepatic injury with coagulopathy and hepatic encephalopathy in a patient without pre-existing hepatic disease (Trey and Davidson 1970), die from increased intracranial pressure while awaiting transplantation (Marion and Bullock 2009). Limited data exist regarding the use of TH for acute hepatic failure because of the low prevalence of the disease, and because of heterogeneity in etiology and treatment. In one case series, 14 patients with acute hepatic failure and severe intracranial hypertension (intracranial pressure > 25 mmHg) were treated with TH for 10 to 118 hours (Jalan et al. 2004). On average intracranial pressure was reduced from 36.5 to 16.3 mmHg and 13/14 patients were able to undergo successful orthotopic liver transplant and had complete neurologic recovery. The US Acute Liver Failure Study Group has stated, "the induction of moderate hypothermia appears to be promising as a bridge to orthotopic liver transplantation," but did not make specific recommendation for its use (Stravitz et al. 2007). TH is used on a case-by-case basis in this population. The prevalence of seizures in patients with acute hepatic failure is reported as a wide range of 2 to 33%, and diagnosis of electrographic seizures may be difficult in this context given the overlap of triphasic waves with rhythmic or periodic epileptiform activity (Abou Khaled and Hirsch 2008, Brenner 2004). cEEG may be useful in this population if clinical suspicion for seizures exists.

Hypothermia Protocols

The implementation of TH should be guided by a local clinical protocol that guides the three major phases of treatment: induction of hypothermia, maintenance of hypothermia, and re-warming. An effective protocol specifies the methods and necessary equipment for each phase, duration of therapy, optimal monitoring, and treatment of side effects.

Cooling methods most commonly used for induction of TH include surface cooling devices, endovascular cooling catheters, infusion of cold intravenous solutions, application of ice packs, and alcohol baths. Intravascular cooling catheters may be more efficacious for induction and maintenance of hypothermia compared to surface cooling devices (Arrich 2007, Pichon et al. 2007). Shivering is a common side effect of TH and introduces electrode movement and muscle artifact. Treatment of shivering facilitates more effective cooling and often requires sedative and/or paralytic medications, or other anti-shivering drugs (Marion and Bullock 2009).

The duration of hypothermia varies according to indication. Cardiac arrest patients are typically cooled for 24 hours whereas TBI and acute hepatic failure patients may be cooled for 2 to 5 days (Marion and Bullock 2009, Jalan et al. 2004). Controlled re-warming may prevent rebound cerebral edema and should occur no faster than 0.25°C/hour (Marion and Bullock 2009, Sinclair and Andrews 2010, Stravitz et al. 2008).

EEG Monitoring

EEG monitoring has a role in the evaluation of the comatose or otherwise encephalopathic adult patient after cardiac arrest. Of patients who survive after initial resuscitation, about 80% experience coma for at least several minutes (Booth et al. 2004). Their outcome is uncertain, and EEG can be used to screen for NCS, to guide antiepileptic treatment in patients with seizures, and to provide additional prognostic information related to neurologic outcome. cEEG serves a similar role after TBI although the prognostic data are less robust (Synek 1988).

EEG Monitoring without Therapeutic Hypothermia—Since the 1950s, studies have demonstrated EEG patterns associated with neurologic outcome in comatose patients after cardiac arrest (Lundervold 1954). Background activity remains one of the most commonly used aspects of the post-anoxic EEG for prognostication. Burst-suppression, severe voltage attenuation (lower than 10 to 20 microvolts in an anterior to posterior bipolar montage), and continuous generalized periodic epileptiform discharges (GPEDs) on a severely voltage attenuated background are strongly associated with poor outcome (Wijdicks et al. 2006). However, these patterns are dynamic. In a study of serial EEG of 50 patients with myoclonus post-arrest, EEG was shown to vary significantly from day-to-day between these so-called “poor prognosis” patterns. Many study patients’ EEGs also showed unfavorable patterns of “alpha and theta coma” – diffuse, disorganized, and unreactive background activity. However, these coma patterns should be interpreted with caution; in prior studies, up to 20% of comatose patients with alpha coma recovered awareness (Young et al. 1994), Thus, repeating the EEG (perhaps with the removal of sedating medication) may be useful to demonstrate more organized background activity and the appearance of reactive patterns.

Reactivity is an important prognostic component of the post-anoxic EEG. Reactivity assesses the functional capacity of the brain’s ascending reticular activating system communication with thalamocortical networks. The presence of reactivity is important and has been incorporated in some EEG grading scales for prognosis (Thenayan et al. 2010). Reactivity is checked by vigorous stimulation of the patient via tactile (e.g., strong nailbed pressure), noxious (e.g., tickling of nares), visual (e.g., eye opening), and auditory (e.g., loud

clapping and yelling) methods and looking for a reproducible change in the background waveform frequency and/or amplitude (Rossetti et al. 2009). Reactivity should be assessed during a 20 to 40 minute EEG study and several times during a long-term EEG study. Muscle or other non-physiologic artifact alone should not support assessment of reactivity.

Clinical seizures are also important in the prognosis of the post-anoxic patient. They occur among post-arrest encephalopathic patients with an incidence of 10 to 40% (Snyder et al. 1980, Krumholz et al. 1988). Most occur within in the first 3 to 5 days after arrest; they most commonly occur with diffuse or multifocal myoclonus, but partial and generalized tonic-clonic seizures have also been reported. Seizures occur more often in comatose or encephalopathic patients and are associated with a worse neurologic outcome (Snyder et al. 1980), Myoclonic status epilepticus is a clinical diagnosis; it consists of unrelenting diffuse myoclonus involving the face, limbs, and torso. It often occurs with stimulation but should also occur spontaneously and continuously. It is strongly associated with poor outcome when onset is in the first 24 hours post-arrest (Wijdicks et al. 2006). Myoclonic status epilepticus often introduces artifact that resembles frontally predominant spike-and-wave discharges of variable amplitude but diffusely present on the EEG. EEG morphology and treatment of post-anoxic seizures will be discussed later in this section. EEG may provide useful prognostic information in comatose patients after cardiac arrest (Young 2000). However, as described in the 2006 meta-analysis supported by the American Academy of Neurology, EEG has a false positive rate for prediction of poor outcome of 3% (95% confidence interval 0.9 to 11%) (Wijdicks et al. 2006).

EEG Usage in Post-Arrest Patients Treated with Therapeutic Hypothermia— Early prognostication has become more difficult because an increasing number of hospitals are providing TH for comatose patients after cardiac arrest and it remains unclear whether predictive factors retain validity when TH is utilized. TH use has led to a greater incidence and duration of sedative and paralytic administration in patients with anoxic encephalopathy. Additionally, TH decreases metabolism of many sedative drugs commonly used in an intensive care unit (Tortorici 2007). TH and increased use of sedatives and paralytics further confounds the prognostic physical examination of comatose patients after cardiac arrest. Sedative administration within twelve hours of physical exam testing for motor response and corneal reflexes has been shown to decrease the specificity of their ability to predict a poor outcome in post-arrest patients (Samaniego et al. 2010).

EEG in the first three days may still be able to identify patterns that associate reliably with poor outcome despite the confounding factors of TH and sedative medications. EEG is not substantially affected at body temperature of 32 to 34°C (Stecker et al. 2001, Michenfelder and Milde 1991). The same EEG patterns associated with poor prognosis in pre-hypothermia studies show similar associations in the few studies available with patients receiving TH. Rossetti et al. (2010) showed using routine EEG that a lack of reactivity was incompatible with good neurologic outcome at least three months after arrest. Another study of 95 patients receiving TH after cardiac arrest showed that a burst-suppression pattern in the first five days of cEEG was incompatible with awakening from coma (Rundgren et al. 2010). Additionally, a continuous background was strongly associated with recovery of awareness. Several quantitative EEG parameters can also be used to discriminate between good and bad outcome in the first 24 hours of EEG monitoring (Wennervirta et al. 2009). Further research in quantitative and qualitative EEG with attention to time of EEG acquisition, concurrent sedation administration, and body temperature is needed.

Seizures and status epilepticus remain common in post-arrest patients treated with hypothermia and may not be clinically detectable when neuromuscular blocking agents are used (Hovland et al. 2006). By pooling together four published studies (Rossetti et al. 2010,

Rundgren et al. 2010, Wennervirta et al. 2009, Legriel et al. 2009) of consecutive post-arrest patients treated with TH who underwent EEG or cEEG in the first 1 to 2 days after cardiac arrest and up to five days after arrest, the calculated prevalence of acute electrographic status epilepticus in post-arrest patients treated with hypothermia is 29% (82/284; 95% confidence interval 23 to 35%). Electrographic seizures typically began within the first two days after cardiac arrest. Although most of the EEGs from these studies derived from 5 to 8 EEG channel studies, these results are similar to a study of 38 consecutive similar adult patients with cEEG (16 to 18 channels) at the Hospital of University of Pennsylvania (personal data). One challenge in interpreting these results stems from the different ways in which the terms “status epilepticus” and “seizures” were defined. The length of time necessary to constitute status epilepticus varied between 5 to 30 minutes in these studies, and some included burst-suppression patterns with sharp activity as seizures. We have seen an ictal clinical correlate with many of the periodic epileptiform discharge patterns > 2 Hz in this patient population.

Acute status epilepticus in post-anoxic patients is very difficult to treat and highly associated with death and poor neurologic outcome despite TH usage (Rossetti et al. 2007). However, when we further examined the pooled data mentioned earlier, 6% (5/82; 95% confidence interval 2 to 14%) of post-anoxic status epilepticus patients treated with TH recovered awareness and survived to six months with neurologic disability varying from minimal to severe. Most of these patients were treated with at least three to four antiepileptic drugs. Additionally, there is a suggestion that patients with seizures occurring from a continuous background are more likely to achieve seizure cessation and recovery of awareness than those with seizures occurring from burst-suppression or a severe voltage attenuated background. We have observed a similar case of good cognitive recovery from post-anoxic status epilepticus and clinical myoclonic status epilepticus in a patient with an early alpha coma background and 3 to 4 Hz GPEDs treated with TH. More research is needed to identify which patients are most likely to benefit from aggressive antiepileptic drug therapy for seizures post-arrest.

cEEG will continue to play a role in the management of adult post-arrest patients treated with TH. It will function best when combined with other modalities of prognostication including the clinical exam, somatosensory evoked potentials, and radiographic data. Current data suggest that in the acute setting, approximately 25% of post-arrest patients treated with TH have frequent epileptiform patterns; most of these occur as status epilepticus and some have clinical correlate. Balancing the need for routine EEG and cEEG after cardiac arrest will require research on the clinical importance of EEG patterns over the first few days post-arrest, the effect of sedative medications on EEGs and the development of epileptiform activity, and the effect antiepileptic drug treatment ultimately has on neurologic outcome of patients with epileptiform patterns.

TECHNICAL CONSIDERATIONS

The authors endorse the modified guidelines for performing pediatric EEGs published by the American Clinical Neurophysiology Society (ACNS 2006). Electrodes are applied using the standard International 10–20 System, or the modified International 10–20 System in neonates. Electrodes are applied with collodion and filled with a long acting gel. Electrode gel is generally replaced every 18 to 24 hours and more frequently, if needed. The head is wrapped with elastic net which allows for ventilation. The head is inspected daily by technologists (and often also by bedside nurses) to evaluate for skin breakdown. If breakdown exists, the nearby electrodes are repositioned and an antibacterial ointment is applied to the affected area. We bundle our electrode wires together by pulling the electrodes through two inch stockinette, and this helps prevent swaying artifact. The amplifier and the patient cable should be placed away from the cooling blanket equipment to

avoid electrical interference. We have also found that the temperature gauge may cause interference and should not make contact with the amplifier or cable.

The skull may have defects from hemicraniectomy for decompression after severe TBI or large stroke. Additionally, patients with severe TBI and large stroke may have intracranial pressure monitors. The skull defects make EEG electrode placement more challenging and introduce breach activity into the EEG. Additionally, since hypothermia may promote functional immunocompromise and possibly a coagulopathic state scalp, checks for signs of infection and bleeding are important.

Many centers place the reference electrode between Fz and Cz which is easily accessed and typically artifact free. The ground electrode should be located in an area unlikely to be disturbed by nursing. Typically we place it on the left or right central region. The ground and reference electrodes are placed approximately four centimeters apart.

Some centers use CT or MRI compatible electrodes that are made of plastic so that images can be obtained with electrodes left in place. This eliminates the need for multiple reconnects which may reduce skin breakdown from multiple applications and removal of electrodes, minimize extra work for the technologist in removing and replacing electrodes for some imaging procedures, and increase the amount of data obtained by reducing time spent disconnected from EEG. There may be an initial increased application time due to short and delicate leads, but after several applications, technologists become proficient. Cleaning time is more time consuming than standard electrodes and the plastic is susceptible to cleaning chemicals which can cause the electrodes to deteriorate. Disposable plastic electrodes are available. Subdermal electrodes are used in some ICU settings. They may be rapid to apply. For long-term use collodion with gauze is generally applied over the subdermal electrode. Clear and followed protocols are required to ensure sterility with universal needlestick precautions.

Artifact may confound interpretation and is particularly common in the intensive care unit setting (Tatum et al. 2011). Artifacts are physiological (related to body function) and nonphysiological (generated from electromagnetic fields outside the body) (White and Van Cott 2010). Physiological artifacts include EMG and movement artifact. With regarding to TH, shivering artifact (muscle and movement) may occur during hypothermia and is important to note since often shivering will be treated with counter-warming or medications. EKG, pulse, and ballistocardiographic artifact can be identified using an EKG channel and synchronized video. Sweat artifact may be present during the re-warming phase. Nonphysiologic artifacts include electrical artifact in the electrically complex ICU environment. Ventilators such as traditional mechanical ventilators or high-frequency oscillators can cause rhythmic artifacts. Patting artifact is especially important to consider in neonates and may mimic electrographic seizures. Other nonphysiological artifacts include medication drips and fluid in the endotracheal tubing. Simultaneous video monitoring can be helpful in differentiating rhythmic artifacts and cerebral rhythmic activity on EEG recordings.

It is important to note events which may impact EEG interpretation. This can easily be done by bedside caregivers using event buttons or written logs, but requires training and frequent reminders. Medications which can affect the mental state and particularly seizure medications should be noted for the EEG reviewer. Noting the time of a seizure medication load can be particularly helpful since this can cause transient slowing or discontinuous activity and can help time-lock seizure timing to antiepileptic loads and levels. The use of mechanical ventilators, oscillators, chest physical therapy, extra-corporeal membrane oxygenation (ECMO), and patient contact (i.e., patting a neonate) may cause rhythmic and/

or electrical artifacts and should be noted. If synchronized video monitoring is not available then a bedside observer is necessary to document clinical events of interest.

Critically ill patients are often surrounded by equipment, with limited space available at bedside. Most new EEG instruments have a small footprint. Alternatively, if used frequently, the equipment can be wall-mounted as in an epilepsy monitoring unit. Placing the equipment carefully is important to ensure caregivers have access to the patient, that the monitor is not excessively bumped or disconnected, and that the patient remains on video.

It is often important to be able to access EEG from multiple sites within the hospital and remotely. This makes review several times per day or when needed more feasible. One option is to use a collector EEG instrument at bedside that is connected by an internal network to an EEG server that can be accessed from multiple sites.

Several issues pertain specifically to neonates. In addition to scalp electrodes, extra-cerebral channels including EKG and respiratory channels should be used. Eye leads and surface EMG leads may be helpful but are not required. Sleep must be captured to adequately assess for encephalopathy in newborns. Therefore, the minimum duration of recordings, even for a routine EEG, has been set by the American Clinical Neurophysiology Society at one hour. However, adequate evaluation of an encephalopathic infant may require one to three hours. For centers conducting selective-head cooling, EEG leads are placed under the cooling cap. Impedance and amplitude issues have not been reported to be significantly affected with the cooling cap. Some neonatal ICUs may use near-infrared spectroscopy (NIRS) to monitor brain oxygenation. The leads for MRS are recommended to be placed bilaterally on the forehead. Minor adjustments in position of the NIRS leads and/or the frontal EEG leads may be necessary to minimize artifact. Other NICUs will want to maintain aEEG recordings while obtaining intermittent or continuous full array EEG recordings. Again, EEG electrode placement may need to be modified as aEEG leads are placed near C3–C4 or C3-P3 and C4-P4. Alternatively, the signal could be split between aEEG and EEG recording devices. Reviewing neonatal ICU EEG recordings also has specific requirements and expertise. Both the gestational age at birth and age of life is necessary to accurately evaluate the age appropriateness of the EEG background for the patient and in some cases to discriminate between immaturity and encephalopathy. Education and training are recommended for EEG technologists or neurophysiologists who have not previously reviewed neonatal EEG recordings.

CONCLUSIONS

Neuroprotective therapies such as therapeutic hypothermia are expanding and for some indications are quickly becoming a standard of care at many institutions. Across age groups, EEG data can be useful in evaluating encephalopathy and identifying seizures. EEG recording procedures may need to be adapted for ICU specific issues. Further research is needed to identify the optimal role for EEG monitoring in patients undergoing TH.

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