QUANTITATIVE EEG FOR SEIZURE IDENTIFICATION

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The Need for Quantitative EEG

Recent studies have shown that many critically ill children and adults experience electrographic seizures and electrographic status epilepticus. Observational studies describe that the incidence of electrographic seizures is 10-30% in cohorts of critically ill children and adults with acute encephalopathy due to numerous conditions. The majority of electrographic seizures in critically ill patients are EEG-only seizures (subclinical seizures or non-convulsive seizures) which would not be identified in the absence of EEG monitoring. As a result, recent guidelines and consensus statements recommend using continuous EEG monitoring in a large number of patients with encephalopathy and acute brain injury to identify electrographic seizures.(Brophy, Bell et al. 2012, Claassen, Taccone et al. 2013, Le Roux, Menon et al. 2014, Herman, Abend et al. 2015, Herman, Abend et al. 2015) Several studies have described rapid increases in the use of continuous EEG monitoring in these cohorts.(Ney, van der Goes et al. 2013, Sanchez, Carpenter et al. 2013, Gavvala, Abend et al. 2014)

Several challenges arise with expanded continuous EEG monitoring use given current practice. First, there is a vast amount of EEG data to review by a limited number of electroencephalographers. Second, electroencephalographers often review data only intermittently, potentially leading to delays between seizure onset and management initiation. Third, despite the fact that critical care medicine providers are more readily available at bedside and experienced in the interpretation and utilization of continuous data monitors, they are generally not able to interpret and act upon conventional EEG data. While review of conventional EEG by expert encephalographers remains the gold standard, more efficient methods are needed to allow electroencephalographers to screen EEGs more quickly and to make EEG monitoring data more readily accessible to bedside caregivers who may be able to act on the EEG data more rapidly.

Quantitative EEG techniques may help solve these problems. First, the conventional EEG data is often time compressed to show 1-2 hours on a screen. This allows rapid review of an extensive amount of data, and allows the electroencephalographer to "zoom-in" on specific areas of interest to review the conventional EEG. Second, rather than displaying multiple channels, a limited number of channels (sometimes limited to right and left hemispheres) can be displayed, and this makes interpretation simpler. Third, the quantitative EEG techniques use components of the EEG such as amplitude or frequency to identify seizures. If seizures involve increases in amplitude and frequency compared to baseline EEG activity, then these changes can be displayed using quantitative EEG techniques such as amplitude integrated (aEEG) EEG or color density spectral array (CDSA). The main quantitative EEG techniques have been reviewed.(Scheuer and Wilson 2004)

Accuracy of Quantitative EEG for Seizure Identification

Several studies have evaluated the accuracy and clinical utility of various quantitative EEG techniques. Overall, the accuracy is dependent on a combination of the quantitative EEG characteristics, user education and experience, and perhaps most importantly, electrographic seizure characteristics in individual patients. Some key studies addressing quantitative EEG techniques and clinical utility are summarized below.

Swisher performed a study evaluating the diagnostic accuracy of a panel of quantitative EEG trends for seizure identification by neurophysiologists and non-neurophysiologists in critically ill adults. The study enrolled 45 critically ill adults including 30 consecutive with non-convulsive seizures identified by conventional EEG monitoring and 15 patients without seizures. Patients with non-convulsive status epilepticus were excluded. The EEGs were acquired with standard international 10-20 electrode placement systems, and quantitative EEG was generated from the conventional EEG. Four EEG panels each displaying one hour of data were created for each patient, yielding 180 total quantitative EEG panels. The panels displayed the rhythmicity spectrogram, CDSA, EEG asymmetry index, and aEEG. The trends used averages from the right and left hemispheres. Seizures were present in 105 of the 180 panels (58%). The panels were reviewed by five neurophysiologists, seven EEG

technologists, and five neuroscience ICU nurses. After a 15 minute training using a PowerPoint presentation, the participants were asked to identify seizures on the quantitative EEG panels. When asked to determine whether each quantitative EEG panel contained seizures, the sensitivity was 84%, specificity 69%, positive predictive value 79%, and negative predictive value 76%. These test characteristics were similar for neurophysiologists, EEG technologists, and ICU nurses. All of the reviewers had poor performance when asked to identify the number of seizures, with only 51% correct. Secondary analysis indicated that: (1) identification of short seizures (less than 25th percentile which was less than 41 seconds) was worse than long seizures (greater than 75th percentile which was greater than 121 seconds), and (2) generalized, bilateral, and hemispheric seizures were identified better than focal seizures. The false-negative rate was 16% indicating some patients with electrographic seizures would not be identified. Additionally, the false-positive rate of 31% indicated that some patients might undergo unnecessary treatment with anti-seizure medications if there was not interim review of conventional EEG to confirm the quantitative EEG findings. The authors concluded that even when used as a panel, quantitative EEG trends did not seem to be sufficient as the sole method for reviewing EEG monitoring data. However, they represented a promising tool to aid in the detection of seizures by neurophysiologists and non-neurophysiologists.(Swisher, White et al. 2015)

Williamson evaluated the sensitivity of CSA for seizure identification in 118 critically ill adults. EEG monitoring was performed using the standard 10-20 system, and CSA was generated from the conventional EEG. Two hours of EEG data were shown per panel, and each panel contained five spectral arrays including left lateral power, left parasagittal power, right lateral power, right parasagittal power, and the relative asymmetry index. Two neurology residents reviewed the quantitative EEG trends and marked segments thought to represent seizure activity. The gold standard was electroencephalographer review of conventional EEG. Seizures were present in 39 of 113 EEG recordings with a median of 20 seizures per recording. Of the 39 patients with seizures, Reviewer 1 identified at least one seizure in 38 patients while Reviewer 2 identified at least one seizure in all 39 patients. Reviewer 1 identified 87% of 1190 seizures and Reviewer 2 identified 91% of 1190 seizures. Reviewers spent on average 10.3 minutes per recording. Overall for both reviewers, for every one seizure identified there were 14 segments that did not contain seizures marked. Combining the two reviewers, 99% of patients with seizures were identified, 89% of total seizures were identified, and 88% of seizures were identified per patient with seizures. This study had asked the reviewers to mark any segment that “might” contain a seizure, and therefore the study design deliberately accepted a higher false-positive rate in order to identify as many seizures as possible. The logic behind that plan was that the final determination regarding seizure presence or absence, and subsequent patient management, would not be based on CSA review alone, but would be by review of the conventional EEG data at the CSA segment of concern. The authors concluded that CSA-guided review could support screening of EEG monitoring data for seizures, but that some patients with seizures might not be identified.(Williamson, Wahlster et al. 2014)

Moura studied the sensitivity and efficiency of CSA screening by neurophysiologists in 118 critically ill adults. There were several groups. First, three neurophysiology fellows performed CSA-guided review in which they reviewed the first 30 minutes of conventional EEGs and then used CSA to guide their subsequent review. They could review the conventional EEG around any suspicious CSA segments. Second, the three neurophysiology fellows performed page-by-page visual review of all the conventional EEG data. Third, two attending neurophysiologists reviewed all of the conventional EEG as a gold standard. Seizures were present in 40 of the 118 patients. There were 2092 hours of EEG monitoring data, and there were 1192 seizures. The displays included two-hours of data on an image, and each image contained five CSA panels including left and right lateral and parasagittal chains and hemispheric asymmetry spectrogram. The average time to perform CSA-guided review (8 +/- 4 minutes) was significantly shorter than the time for conventional EEG review (38 +/- 17 minutes). CSA-guided review identified all patients with seizures and identified 87% of individual seizures. No patients with electrographic status epilepticus went undetected by CSA-guided review. All seizures lasting more than five minutes were detected by CSA-guided review. Excluding cases with electrographic status epilepticus, CSA-guided review was less likely to identify patients with more seizures or with shorter seizures (< 1 minute). The authors concluded that CSA-guided EEG review could enable significantly faster EEG interpretation without loss of sensitivity for critical findings in the vast majority of patients.(Moura, Shafi et al. 2014)

Dericioglu evaluated the use of quantitative EEG displays by non-experts for seizure identification in adults. Consecutive patients underwent EEG monitoring using the standard 10-20 system. For the spectrogram displays, electrode pairs were selected that would best reflect the ictal activity identified on the conventional EEG. These EEG recordings were paired with control tracings showing the same electrode pairs but without seizures present

on conventional EEG. The quantitative EEG displays contained amplitude integrated EEG and DSA. Participants included one Critical Care Neurology fellow, one Neurology resident, and two Neuro ICU nurses. The participants had training sessions lasting 5-6 hours describing theoretical knowledge and examples of the traces. Each of the participants reviewed 20 traces from 10 seizure patients with seizures and 10 controls. They were asked to identify each seizure. The seizure group included 289 hours of EEG with 700 seizures. The seizure count per recording was 10-182. Among the 700 seizures, 63% were recognized by all participants, 15% by three participants, 11% by two participants, and 8% by one participant. Raters identified non-convulsive status epilepticus patients with 100% sensitivity. The overall sensitivity and specificity for seizure detection were 93% and 91% respectively in the non-convulsive status epilepticus group. For the seizure and control groups together, the sensitivity and specificity were 93% and 95%, respectively. In the group with seizures, there were 0.5 false seizure alerts per hour. In the group without seizures, there were 0.17 false seizure alerts per hour. The different participants were not significantly different in their accuracy. The authors concluded that non-expert users could achieve acceptable accuracy for seizure identification using quantitative EEG trends following training.(Dericioglu, Yetim et al. 2015)

Haider evaluated the sensitivity and false positive rates of a panel of QEEG for seizure identification in 15 critically ill adults. Nine neurophysiologists reviewed the conventional EEG to identify seizures as the gold standard. Nine separate neurophysiologists reviewed 6-hour epochs of QEEG, with and without a channel of raw EEG. The mean sensitivity for seizure identification ranged from 51-67% for QEEG-only and 63–68%for QEEG plus one channel of conventional EEG. The false positive rare ranged from 1/hour for QEEG-only to 0.5/hour for QEEG plus one channel of conventional EEG. Epochs with the highest sensitivities contained frequent, intermittent seizures. Epochs with lower sensitivities contained slow frequency and low amplitude seizures or contained rhythmic or periodic patterns. The median review time was significantly shorter for QEEG (6 minutes) and QEEG plus one channel of conventional EEG (15 minutes) than for conventional EEG (19 minutes). The authors concluded that a QEEG panel could shorten the time for EEG review with reasonable sensitivity and low false positive rare. The presence of some false positives led to the conclusion that the conventional EEG would need to reviewed along with QEEG.(Haider, Esteller et al. 2016)

Stewart evaluated CDSA and aEEG use by clinical neurophysiologists in critically ill children. Records were obtained using full array EEG monitoring and then converted to 8 channel double-distance montages containing CDSA for aEEG. Eight hours were displayed per screen. There were 27 recordings of which 17 contained seizures. Three neurophysiologists underwent two hours of training and then reviewed the quantitative EEG tracings with CDSA and aEEG reviewed separately. The neurophysiologists identified a median of 83% of seizures per recording using CDSA and 81.5% of seizures per recording using aEEG. The median seizure identification rate was 75% or greater among 59% of recordings using CDSA and 65% of recordings using aEEG. Overall, 10.5% of seizures were completely missed by all three reviewers on both CDSA and aEEG displays. Significantly more seizures were missed with CDSA (21%) than aEEG (14%). Missed seizures were generally low voltage (<75 microvolts), short duration (<1 minute), remained focal, or occurred in the context of epileptiform discharges in the background. The false-positive rate was 1 per 17 hours of CDSA and 1 per 20 hours of aEEG. There was substantial agreement among all neurophysiologists with CDSA (kappa 0.78) and moderate agreement with aEEG (kappa 0.54). The authors concluded that CDSA and AEEG are useful screening tools by trained neurophysiologists, but these techniques would not replace careful review of conventional EEG data.(Stewart, Otsubo et al. 2010)

Pensirikul described CDSA for seizure identification by neurophysiologists in critically ill children. Conventional EEGs from 21 children were obtained using the conventional 10-20 system and were reviewed by two electroencephalographers as the gold standard. Seizures were present in 43% of subjects, and there were 72 total seizures. The first eight hours of each subject's EEG was converted to CDSA display which included eight channels of double distance CDSA with two hours per screen. There were 84 total images (21 patients x 4 images per patient). The images were reviewed by eight pediatric encephalographers after reviewing a brief training manual. Four participants (group A) reviewed the 84 images in random order. Four participants (group B) were told whether seizures occurred in the initial 30 minutes and then reviewed the subsequent images from each subject in the appropriate order. Specificity was 92% and 78% for groups A and B, respectively. Sensitivity was 65% and 75% for groups A and B, respectively. 10% of images were falsely classified as containing a seizure and among those images the mean false-positive rate was 1.5 per hour. In terms of seizure identification, 21.5% of seizures were identified by all eight raters, 24.6% of seizures were identified by seven raters, and 9.2% of seizures were identified by no raters. Seizures lasting more than two minutes were more likely to be identified.

The authors concluded that CDSA could be a useful screening tool for seizure identification by electroencephalographers, but it would not identify all seizures and false-positives occur.(Pensirikul, Beslow et al. 2013)

Topjian evaluated the use of CDSA to identify seizures in 39 children resuscitated from cardiac arrest by Critical Care Medicine providers. EEG monitoring was performed with a standard 10-20 system. A pediatric encephalographer scored the EEG as containing no seizures, seizures or status epilepticus. One-hundred CDSA images included hemispheric right and left displays of CDSA with two hours per screen. The seizure prevalence of 30%. The participants included 39 Critical Care Medicine providers including 12 attendings, 8 fellows, and 19 nurses. They underwent a 15 minutes standardized training with a PowerPoint tutorial. CDSA images were presented in replication so each participant saw 200 images in random order. Participants scored each image as containing or not containing a seizure, and they were not asked to distinguish seizures from status epilepticus or to identify individual seizures. Overall, the Critical Care Medicine providers had a seizure detection sensitivity of 70%, specificity of 68%, positive predictive value of 46%, and negative predictive value of 86%. The kappa was 63% for all images and 69% for images with seizures. The three Critical Care Medicine provider groups (attendings, fellows, and nurses) performed similarly. The authors concluded that CDSA use by critical care medicine providers had a high negative predictive value and moderate sensitivity.(Topjian, Fry et al. 2015)

Data Summary

Overall, these studies have yielded generally similar results whether performed in critically ill adults and children, with quantitative EEG reviewed by electroencephalographers or critical care medicine providers, with varying training approaches and training durations, with varying quantitative EEG trends, and with a varying number of quantitative EEG channels. Sensitivity is imperfect meaning that while many seizures are identified using these techniques, some seizures are not identified. Additionally, specificity is imperfect indicating some patients might be incorrectly diagnosed has having seizures, potentially leading to overtreatment and exposure to unnecessary anti-seizure medications. Seizures which are focal, lower in amplitude or frequency, or shorter duration are not identified as well using quantitative EEG techniques.

A 2016 survey of members of the American Clinical Neurophysiology Society regarding QEEG yielded responses from 75 neurophysiologists who used QEEG in their practice. Interpretation was generally by neurophysiologists and neurophysiology fellows (97% and 52%, respectively), but 21% reported use by non-neurophysiologists. Further 22% of non-neurophysiologists were reported to use the QEEG data to directly guide clinical care. QEEG was used most frequently for seizure detection (92%) and burst suppression monitoring (59%). Less common uses included monitoring the depth of sedation (29%), ischemia detection (28%), vasospasm detection (28%) and prognosis after cardiac arrest (21%). When QEEG is used, about half of respondents did not review every page of conventional EEG. Respondents indicated substantial variability in the preferred QEEG trends for seizure and ischemia detection.(Swisher and Sinha 2016)

Considerations for Use

Rather than being developed as a stand-alone technique as occurs with some amplitude integrated EEG monitoring in neonates, most work regarding quantitative EEG trends in critically ill children and adults has viewed these as adjuvants to conventional EEG. The electroencephalographer or bedside caregiver might identify suspicious regions using quantitative EEG approaches and then selectively review the conventional EEG to confirm the presence or absence of seizures before initiating management. This quantitative EEG guided review might make electroencephalographer and EEG technologist review of full array conventional EEG more efficient. Additionally, at institutions with only periodic interpretation by EEG technologists or electroencephalographers, bedside caregivers might aim to use quantitative EEG during periods without conventional EEG review available, but have confirmatory EEG interpretation of any concerning quantitative EEG patterns prior to therapeutic interventions. This would allow limited EEG interpretation resources to be directed to the segments of EEG that might be the most beneficial. Health systems without conventional EEG interpretation resources might be able to use bedside quantitative EEG techniques, albeit imperfectly, to at least provide some information. This approach has been adopted by many Neonatal Intensive Care Units using aEEG since despite the recognized inaccuracies of amplitude integrated EEG, the tool is readily available to bedside caregivers and does not depend on electroencephalographer availability.

References

Brophy, G. M., R. Bell, J. Claassen, B. Alldredge, T. P. Bleck, T. Glauser, S. M. Laroche, J. J. Riviello, Jr., L. Shutter, M. R. Sperling, D. M. Treiman, P. M. Vespa and C. Neurocritical Care Society Status Epilepticus Guideline Writing (2012). "Guidelines for the evaluation and management of status epilepticus." Neurocrit Care **17**(1): 3-23.

Claassen, J., F. S. Taccone, P. Horn, M. Holtkamp, N. Stocchetti and M. Oddo (2013). "Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM." Intensive Care Med **39**(8): 1337-1351.
Dericioglu, N., E. Yetim, D. F. Bas, N. Bilgen, G. Caglar, E. M. Arsava and M. A. Topcuoglu (2015). "Non-expert use of quantitative EEG displays for seizure identification in the adult neuro-intensive care unit." Epilepsy Res **109**: 48-56.

Gavvala, J., N. Abend, S. LaRoche, C. Hahn, S. T. Herman, J. Claassen, M. Macken, S. Schuele, E. Gerard and E. E. G. M. R. C. Critical Care (2014). "Continuous EEG monitoring: a survey of neurophysiologists and neurointensivists." Epilepsia **55**(11): 1864-1871.

Haider, H. A., R. Esteller, C. D. Hahn, M. B. Westover, J. J. Halford, J. W. Lee, M. M. Shafi, N. Gaspard, S. T. Herman, E. E. Gerard, L. J. Hirsch, J. A. Ehrenberg, S. M. LaRoche and E. E. G. M. R. C. Critical Care (2016). "Sensitivity of quantitative EEG for seizure identification in the intensive care unit." Neurology **87**(9): 935-944.

Herman, S. T., N. S. Abend, T. P. Bleck, K. E. Chapman, F. W. Drislane, R. G. Emerson, E. E. Gerard, C. D. Hahn, A. M. Husain, P. W. Kaplan, S. M. LaRoche, M. R. Nuwer, M. Quigg, J. J. Riviello, S. E. Schmitt, L. A. Simmons, T. N. Tsuchida and L. J. Hirsch (2015). "Consensus statement on continuous EEG in critically ill adults and children, part II: personnel, technical specifications, and clinical practice." J Clin Neurophysiol **32**(2): 96-108.

Herman, S. T., N. S. Abend, T. P. Bleck, K. E. Chapman, F. W. Drislane, R. G. Emerson, E. E. Gerard, C. D. Hahn, A. M. Husain, P. W. Kaplan, S. M. LaRoche, M. R. Nuwer, M. Quigg, J. J. Riviello, S. E. Schmitt, L. A. Simmons, T. N. Tsuchida, L. J. Hirsch and E. E. G. T. F. o. t. A. C. N. S. Critical Care Continuous (2015). "Consensus statement on continuous EEG in critically ill adults and children, part I: indications." J Clin Neurophysiol **32**(2): 87-95.

Le Roux, P., D. K. Menon, G. Citerio, P. Vespa, M. K. Bader, G. M. Brophy, M. N. Diringer, N. Stocchetti, W. Videtta, R. Armonda, N. Badjatia, J. Boesel, R. Chesnut, S. Chou, J. Claassen, M. Czosnyka, M. De Georgia, A. Figaji, J. Fugate, R. Helbok, D. Horowitz, P. Hutchinson, M. Kumar, M. McNett, C. Miller, A. Naidech, M. Oddo, D. Olson, K. O'Phelan, J. J. Provencio, C. Puppo, R. Riker, C. Robertson, M. Schmidt and F. Taccone (2014). "Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine." Neurocrit Care **21 Suppl 2**: S1-26.

Moura, L. M., M. M. Shafi, M. Ng, S. Pati, S. S. Cash, A. J. Cole, D. B. Hoch, E. S. Rosenthal and M. B. Westover (2014). "Spectrogram screening of adult EEGs is sensitive and efficient." Neurology **83**(1): 56-64.

Ney, J. P., D. N. van der Goes, M. R. Nuwer, L. Nelson and M. A. Eccher (2013). "Continuous and routine EEG in intensive care: utilization and outcomes, United States 2005-2009." Neurology **81**(23): 2002-2008.

Pensirikul, A. D., L. A. Beslow, S. K. Kessler, S. M. Sanchez, T. A.A., D. J. Dlugos and N. S. Abend (2013). "Density Spectral Array for Seizure Identification in Critically Ill Children." Journal of Clinical Neurophysiology **30**(4): 371-375.

Sanchez, S. M., J. Carpenter, K. E. Chapman, D. J. Dlugos, W. B. Gallentine, C. C. Giza, J. L. Goldstein, C. D. Hahn, S. K. Kessler, T. Loddenkemper, J. J. Riviello, Jr., N. S. Abend and E. E. G. G. Pediatric Critical Care (2013). "Pediatric ICU EEG monitoring: current resources and practice in the United States and Canada." J Clin Neurophysiol **30**(2): 156-160.

Scheuer, M. L. and S. B. Wilson (2004). "Data analysis for continuous EEG monitoring in the ICU: seeing the forest and the trees." J Clin Neurophysiol **21**(5): 353-378.

Stewart, C. P., H. Otsubo, A. Ochi, R. Sharma, J. S. Hutchison and C. D. Hahn (2010). "Seizure identification in the ICU using quantitative EEG displays." Neurology **75**(17): 1501-1508.

Swisher, C. B. and S. R. Sinha (2016). "Utilization of Quantitative EEG Trends for Critical Care Continuous EEG Monitoring: A Survey of Neurophysiologists." J Clin Neurophysiol **33**(6): 538-544.

Swisher, C. B., C. R. White, B. E. Mace, K. E. Dombrowski, A. M. Husain, B. J. Kolls, R. R. Radtke, T. T. Tran and S. R. Sinha (2015). "Diagnostic Accuracy of Electrographic Seizure Detection by Neurophysiologists and Non-Neurophysiologists in the Adult ICU Using a Panel of Quantitative EEG Trends." J Clin Neurophysiol **32**(4): 324-330.

Topjian, A. A., M. Fry, A. F. Jawad, S. T. Herman, V. M. Nadkarni, R. Ichord, R. A. Berg, D. J. Dlugos and N. S. Abend (2015). "Detection of electrographic seizures by critical care providers using color density spectral array after cardiac arrest is feasible." Pediatr Crit Care Med **16**(5): 461-467.

Williamson, C. A., S. Wahlster, M. M. Shafi and M. B. Westover (2014). "Sensitivity of compressed spectral arrays for detecting seizures in acutely ill adults." Neurocrit Care **20**(1): 32-39.