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COMMENT

Continuous EEG monitoring still recommended for neonatal seizure management: commentary on NEST trial

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We read with interest the report of the Newborn Electrographic Seizure Trial (NEST) comparing treatment of clinically evident seizures (clinical seizure group (CSG)) vs. electrographic seizures detected by amplitude-integrated electroencephalography (aEEG) (electrographic seizure group (ESG)), which aimed to answer the question: "should all electrographic seizures, even without a clinical correlate, be treated to reduce the risk of subsequent impairment, or do the treatments themselves contribute to neurological disruption and injury?"[1] The results of the trial showed that children who were treated based on aEEG results did not have lower rates of death or disability (primary outcome) but the authors "report an association of improved cognitive outcomes at 2 years in the CSG."

As for the two similar but smaller trials published earlier,[2,3] enrollment, data collection, and analysis in the NEST study was challenging and resulted from the efforts of many investigators at their 13 sites. Ultimately, the trial of Hunt et al. was terminated early after publication of the trial conducted in St. Louis that suggested benefit from treatment of electrographic seizures, leading to loss of equipoise among the investigators. The effect of this publication was that it precluded enrollment of the planned 300 subjects per group (instead of the reported 106 per group) that would have yielded more statistical power. Although we agree that it is important for the authors to publish the results of their trial, we offer commentary regarding the trial design and data presented to express caution about the study's conclusions.

In particular, we are concerned that some may conclude that this study shows harm of antiseizure medication (ASM) treatment of electrographic seizures and that the use of aEEG or conventional video-EEG (cvEEG) monitoring is not necessary. Indeed, the American Clinical Neurophysiology Society and International League Against Epilepsy have both stated that cvEEG is the gold standard for accurate diagnosis of neonatal seizures and therefore should be used to guide treatment when available.[4,5] These recommendations are based on a wealth of data showing that cvEEG is critical to distinguish epileptic from non-epileptic paroxysmal events in newborns.

Most importantly, we think that the data presented in this paper do not support its conclusions and should be interpreted with caution, for several reasons. First, the authors did not report a statistically significant difference in the amount of ASMs given to either group. Presuming this was the case, the discussion of ASMs being potentially harmful is irrelevant to whether clinical or electrographic seizures were treated in this trial. The ASMs administered could not be implicated in causing worse cognitive outcome in the ESG if the amount of ASM administered was similar for both groups.

A second potential explanation for why the ESG had a slightly worse cognitive outcome is that seizure severity may have differed between groups. We have several concerns about the analysis of seizure severity in this trial, which was reported as total seconds of seizures measured over three different time periods (total aEEG recording, per day of total aEEG recording, and 12–72 h of age). Seizure severity has been measured in seizures in minutes/hour of EEG recording time in other studies,[6,7] which reflects both the intensity of seizures and actual EEG/aEEG recording time (since EEG/aEEG may be interrupted for various reasons and durations). Episodes of status epilepticus are another important indicator of seizure severity but were not reported in this trial. Additionally, the authors described that "Seizure burden in seconds was calculated for each participant for as long as the aEEG monitor was attached." Although seizure burden was calculated for three different time periods, the duration of aEEG recording could have affected any/all of these measures, yet was not reported. The authors compared mean seizure burden between groups for two of the three measures (per day and 12–72 h), but the distribution of seizure burden is often skewed[7] so the use of median [interquartile range] may have been the more suitable measure. Finally, the timing of aEEG initiation is also a critical variable influencing determination of total seizure burden and treatment success since seizure burden can be high in the first hours after seizure onset, yet aEEG start time was not reported.[8] Accurate measurement of seizure burden is particularly important since seizure severity/burden is a major factor affecting ASM efficacy[7,9] and a determinant of outcome for neonates with hypoxic–ischemic encephalopathy (HIE).[10]

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Third, the main difference in median cognitive scores (i.e., 97 vs. 101) mentioned in the conclusion was quite small, even if statistically significant, and these mean scores were within the normal range, which is unexpected for neonates with seizures. Since these scores are higher than for other similar trials,[2,3] the neonatal seizures and/or underlying disorders may have also been less severe. No data were provided describing severity of encephalopathy, aEEG background patterns, or other similar measures of severity of neurologic illness to allow specific comparison with other studies.

Finally, the inclusion of neonates with seizures of all types was pragmatic but introduces the potential for genetic or other etiologies to affect neurologic outcome in either direction, independent of seizure treatment approach. Neonatal genetic epilepsies require a different treatment approach than acute provoked seizures, so the research question addressed in this trial does not apply to this subset of neonates.

We note that another commentary published regarding this trial also emphasized the importance of continuous EEG monitoring for neonatal seizure management and listed some limitations of the trial.[11] We largely agree with this commentary, but we include a more detailed critique of the NEST study design and data analyses to make our argument that the study's conclusions are not supported by the NEST data (i.e., inclusion of all seizure etiologies, issues related to determination of seizure burden, and concerns regarding the primary outcome data). We agree that measurement of seizure burden soon after seizure onset is critical for accurate estimation of overall seizure burden and note that Hunt et al. reported seizure burden measured from as early as 12 h of age. Although subjects were randomized at a mean of ~27 h, there is likely a skewed distribution of age at randomization with subjects with infection, stroke, or genetic etiologies randomized at a much older age than those with HIE, since seizure onset typically occurs at >24 h for etiologies other than HIE. In addition, the NEST study protocol described their process for aEEG review in their Supplement and inclusion of a seizure detection algorithm.

Unfortunately, this and other similar trials have not definitively answered the question of whether all electrographic seizures in neonates should be treated or whether there is a point at which additional ASM treatment may cause more harm than good. Given the limitations described above, we believe it cannot be concluded that there were clinically important differences between groups that should alter current recommendations regarding EEG monitoring[4,5] or treatment of neonatal seizures. Treatment of clinical seizures without use of EEG monitoring has been shown to result in both over- and under-treatment of seizures,[6] while introduction of continuous video-EEG monitoring has been shown to improve the accuracy of seizure detection and decrease mean ASM burden. Thus, while we agree with the authors that more data are clearly needed to determine the efficacy and safety of ASMs for the treatment of neonatal seizures, we strongly advocate for the use of cvEEG monitoring whenever possible for accurate diagnosis of seizures and assessment of ASM treatment effect.

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ADDITIONAL INFORMATION

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