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An ounce of prevention but less than a pound of cure: seizure prophylaxis after intracranial hemorrhage

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The prevention, detection, and management of seizures following acute brain injury in critically ill children continues to be a major challenge in pediatric neurocritical care. With the advent of continuous video electroencephalogram monitoring (EEG) in pediatric intensive care units, the identification of seizures in patients with suspected brain injury has increased [1, 2]. Traumatic brain injury and post-cardiac arrest encephalopathy have been the two most commonly studied etiologies, with the incidence of early post-traumatic seizures in children ranging between 9%–23% [3–5]. Reported risk factors for early post-traumatic seizures have included younger age, injury severity, and presence of cerebral edema [4]. The variability in the incidence across different studies can be attributed to multiple factors including differences in the age of study populations, variability in the use of seizure prophylaxis, and variability in the frequency and duration of continuous EEG monitoring.

In this month's Pediatric Critical Care Medicine, Bansal et al report on the incidence of acute seizures in a single center retrospective cohort of children aged 2 weeks – 2 years who presented with supratentorial intracranial hemorrhage (ICH) on brain imaging between 2008–2013 [6]. The authors identified 72 patients who met inclusion criteria (all neonates, premature infants, and children with a known history of seizures were excluded). The majority of the study population (83%, n=60) had ICH due to traumatic injury, and 60% of the traumatic injuries (36 of 60) were thought to be due to non-accidental trauma. As part of their institutional protocol, all patients were initiated on an antiepileptic drug (AED) at the time of diagnosis for seizure prophylaxis. The choice of AED was left to the discretion of the physician. Also per institutional protocol, 45 patients who were encephalopathic on admission underwent continuous video EEG monitoring for the first 48 hours of admission. Acute seizures, defined as clinical or electrographic seizures in the first 7 days, were

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observed in 40% of patients. Younger age and evidence of parenchymal injury were found to be independent risk factors for acute seizures. Late seizures, defined as any seizure activity 7 or more days after ICH, were found in 11 (17%) of survivors, all of whom continued to receive ongoing treatment with AEDs at outpatient follow-up. Of note, 12% (5 of 43 patients) of patients with late seizures did not have acute seizures during their first week of hospitalization. All patients with late seizures were described as having parenchymal injury diagnosed by brain imaging at the time of initial presentation for ICH. Neither early nor late seizures were found to have an association with in-hospital mortality.

One of the challenges in understanding the epidemiology of early seizures following acute brain injury is the role of seizure prophylaxis. The evidence for post-traumatic seizure prophylaxis in children is weak, leading to variability in its utilization. This confounds epidemiologic studies of seizure incidence following acute brain injury [7, 8]. A strength of the current study is that all children received seizure prophylaxis upon diagnosis of ICH. Despite appropriate loading doses and therapeutic level monitoring, the authors observed a surprisingly high incidence rate of 40% for early seizures. Unfortunately, the choice of AED was not protocolized and was left to the discretion of the clinical team resulting in younger patients frequently receiving (fos)phenytoin and older infants receiving levetiracetam. Younger infants in this study were found to be at higher risk for early seizures, which could be attributed to multiple factors including an increase susceptibility of the younger brain to seizures and the possibility of decreased efficacy of (fos)phenytoin in very young infants. Fewer patients had break-through seizures on levetiracetam prophylaxis compared to phenobarbital and (fos)phenytoin, but this did not reach statistical significance. Of interest, 83% of patients with acute seizures required 2 or more AEDs to achieve seizure control. From these data it seems clear that the ideal medication for seizure prophylaxis in children with ICH, let alone dose and duration, remains unclear.

Sadly, this study both highlights the uncertainty as to how antiepileptic medications can be best used as part of early treatment for ICH as well as the imperative to find an answer. Despite clinically appropriate doses of AEDs initiated promptly at the time of diagnosis, 40% of patients had break-through seizures in the first week of hospitalization. Of perhaps even greater concern, 59% of the acute seizures were electrographic only. This may be an underestimate of the true number of seizures in the study population, as only the subset of patients encephalopathic on admission had continuous EEG monitoring. While there continues to be controversy as to the short- and long-term clinical relevance of nonconvulsive, electrographic seizures [9–12], parenchymal injury and electrographic seizures were significantly associated with the development of late seizures in the current study. If nonconvulsive, electrographic seizures are important, then the timing of their presentation in this study should be noted: the mean time of presentation was 1.9 days ($\pm$ 1.6 days) after ICH. This certainly corroborates other studies of critically ill patients that have demonstrated frequent detection of seizures in critically ill children well beyond the first 24 hours of presentation [13, 14]. It seems as though this study offers yet another opportunity for the critical care community to consider the importance of nonconvulsive seizures, and embark on definitive study as to the best way to prevent, detect, and treat these events. This appears to be particularly relevant for the members of our community who study traumatic brain injury, given the large proportion of children with traumatic brain injury in this study,

and the number of additional reports by others of a high incidence of early seizures in patients with non-accidental trauma [15, 16].

In the end, the data presented by Bansal et al highlight the weaknesses in our current understanding of how best to detect and treat seizures associated with intracranial hemorrhage in early childhood. Seizure prophylaxis in this population failed to prevent seizures in 40% of patients. The ultimate significance of this failure for the patients during their recovery remains unclear. However, given the association between acute and late seizures, which in turn may cause significant ongoing morbidity, the need to find appropriate therapies to prevent early seizures remains. Although standard dosing of AEDs upon admission may not, in isolation, be the ‘ounce of prevention worth a pound of cure’, the results of this study remind us to remain vigilant in our pursuit of the right prevention.

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