

NONCONVULSIVE SEIZURES IN TRAUMATIC BRAIN INJURY: WHAT YOU DON'T SEE CAN HURT YOU

Nonconvulsive Electrographic Seizures after Traumatic Brain Injury Result in a Delayed, Prolonged Increase in Intracranial Pressure and Metabolic Crisis. Vespa PM, Miller C, McArthur D, Eliseo M, Etchepare M, Hirt D, Glenn TC, Martin N, Hovda D. *Crit Care Med* 2007; [Epub ahead of print]. **OBJECTIVE:** To determine whether nonconvulsive electrographic post-traumatic seizures result in increases in intracranial pressure and microdialysis lactate/pyruvate ratio. **DESIGN:** Prospective monitoring with retrospective data analysis. **SETTING:** Single center academic neurologic intensive care unit. **PATIENTS:** Twenty moderate to severe traumatic brain injury patients (Glasgow Coma Score 3–13). **MEASUREMENTS AND MAIN RESULTS:** Continuous electroencephalography and cerebral microdialysis were performed for 7 days after injury. Ten patients had seizures and were compared with a matched cohort of traumatic brain injury patients without seizures. The seizures were repetitive and constituted status epilepticus in seven of ten patients. Using a within-subject design, post-traumatic seizures resulted in episodic increases in intracranial pressure (22.4 ± 7 vs. 12.8 ± 4.3 mm Hg; $p < .001$) and an episodic increase in lactate/pyruvate ratio (49.4 ± 16 vs. 23.8 ± 7.6 ; $p < .001$) in the seizure group. Using a between-subjects comparison, the seizure group demonstrated a higher mean intracranial pressure (17.6 ± 6.5 vs. 12.2 ± 4.2 mm Hg; $p < .001$), a higher mean lactate/pyruvate ratio (38.6 ± 18 vs. 27 ± 9 ; $p < .001$) compared with nonseizure patients. The intracranial pressure and lactate/pyruvate ratio remained elevated beyond postinjury hour 100 in the seizure group but not the nonseizure group ($p < .02$). **CONCLUSION:** Post-traumatic seizures result in episodic as well as long-lasting increases in intracranial pressure and microdialysis lactate/pyruvate ratio. These data suggest that post-traumatic seizures represent a therapeutic target for patients with traumatic brain injury.

COMMENTARY

Nonconvulsive seizures are common in critically ill patients. In fact, multiple studies have demonstrated that the majority of seizures occurring in these patients are nonconvulsive and can only be recognized via EEG monitoring (1). Are they harmful? Although no class I or II trials have been performed to date, there is substantial evidence that they may be harmful, particularly in the injured brain. Vespa and colleagues continue to contribute meaningfully to this literature in the current report.

In the current article, the authors compared ten patients with traumatic brain injury and seizures to ten other traumatic brain injury patients without seizures; the two groups were matched for head CT findings, age, and Glasgow coma score. All seizures happened to be nonconvulsive, and all patients received prophylactic phenytoin for 7 days. Rigorous neurological/neurosurgical intensive care unit (NICU) treatment was applied, with careful management of intracranial pressure [goal <20], cerebral perfusion pressure [kept at >60], jugular venous O_2 saturation [kept at 60–70%], and temperature [kept at 37–37.6°C], with sedation maintained with propofol. EEG was recorded with 12 electrodes, continuously displayed at the bedside, and reviewed a minimum of three times daily. Total power trending software also was used and displayed at the bedside to aid in recognition of possible seizures,

though raw EEG tracings always were reviewed for definitive diagnosis. Intracranial pressure and intracerebral microdialysis (a measure of metabolites in the parenchymal interstitial fluid) data were obtained hourly as part of routine clinical care at the center.

The results demonstrated that nonconvulsive seizures (often associated with periodic discharges as well) corresponded with higher intracranial pressure and higher brain lactate/pyruvate ratio (LPR; see following description for significance), often reaching abnormal levels (i.e., >20 mm Hg and >40 , respectively). The timing of these elevations correlated with the presence of seizures, based on averaging the hourly samples over 12-hour epochs. Interestingly, there was a bimodal peak occurrence of seizures at 29- and 140-hours postinjury. Ictal intracranial pressure (during the 12-hour period beginning with seizure onset) was an average of 12 mm Hg higher than pre-ictal, and ictal LPR was double that of pre-ictal LPR on average. Elevated glutamate also was seen around the time of seizures, averaging 13.1 in the 12-hour designated ictal period versus 2.6 interictally ($p < 0.001$). Mortality and Glasgow Outcome Score outcomes did not differ significantly between the seizure and nonseizure groups.

These results add to the growing evidence that seizures, including nonconvulsive ones, are harmful to humans. Prior evidence includes the following:

- The delay to diagnosis and duration of nonconvulsive status epilepticus are each independent predictors of worse outcome (2).

- The presence of either nonconvulsive seizures or periodic discharges is an independent predictor of worse outcome in multiple patient populations (1).
- In patients with epilepsy but without acute brain injury, prolonged nonconvulsive seizures can lead to permanent neurological injury, albeit rarely (3).
- Neuron-specific enolase, a marker of neuronal injury, can be elevated after nonconvulsive status epilepticus, even without acute brain injury (4).
- In patients with intracerebral hemorrhage, nonconvulsive seizures were associated with increased mass effect and shift on imaging, worsening neurological examination, and a trend toward worse outcome in one study (5), and expanding hemorrhages, with a trend toward worse outcome in another (6).
- Seizure activity can cause elevations in glutamate that reach neurotoxic levels (7) and delayed elevations in glycerol, suggesting membrane breakdown (8).
- Seizures are associated with peri-injury depolarizations (similar or identical to cortical spreading depression), another likely contributor to secondary neuronal injury after an acute brain insult (9).

The evidence of the damaging effects of nonconvulsive seizures in animal studies includes the following:

- Seizures are associated with increases in blood flow, metabolism, excitatory amino acid levels, and lactate.
- In a controlled, rat middle cerebral artery occlusion model, nonconvulsive seizures were associated with larger infarcts and a tripling of mortality (10).
- In a rat low-dose pilocarpine model, nonconvulsive status epilepticus was found to result in long-term motor deficits and impaired social behavior (11).

In contrast, the aggressive treatment often required to stop nonconvulsive seizures in critically ill patients is also potentially harmful (12), leaving room for ongoing controversy and appropriate variations in approach to management.

Elevated intracranial pressure remains a major issue in the management of patients with traumatic brain injury. In many academic NICUs, invasive multimodality monitoring of patients with a variety of acute brain injuries is a common practice, including monitoring intracranial pressure, brain tissue oxygen tension, cerebral blood flow, brain temperature, jugular venous oxygen saturation, and multiple metabolic parameters via cerebral microdialysis. These invasively obtained data are interpreted in conjunction with the usual vital signs, EEG (especially in the past couple years), and physical examination. Cerebral microdialysis was approved for clinical use by the United States Food and Drug Administration in 2002, and

an international consensus statement supporting its use was published in 2004 (13). The most reliable measure of neuronal stress appears to be the LPR—a measure of the redox state of the brain. There are two types of elevation in LPR: ischemic (type I, with prominent elevation in lactate) and nonischemic (type II, with drop in pyruvate). The type II changes often have remained unexplained, but to date, most studies in published literature on cerebral microdialysis did not obtain concomitant EEG recordings.

The limitations of the study by Vespa and colleagues include the relatively small number of patients, the widely spaced sampling (hourly), the lack of clear definition of an electrographic seizure (not a trivial issue), the lack of any sample EEG tracings, and the nonrandomized nature of this retrospective study. Reporting on the relative utility of the quantitative EEG and bedside review (i.e., how often seizures were detected via these techniques) would have been quite useful. Data on the effect of treatment on intracranial pressure and LPR also would have been valuable—do they normalize when seizures stop? If so, how quickly? Finally, as the authors point out, intracranial recordings may show much more extensive epileptic activity than seen on scalp EEG. In fact, a recent report, using miniature intracranial transcortical depth electrode recordings in NICU patients requiring invasive monitoring, provides preliminary evidence to support this theory (14).

Despite these limitations, this is the largest and best investigation into the acute physiologic effects of nonconvulsive seizures in acute brain injury. The authors' conclusions that these data "confirm a long-held, but previously unsupported, premise that electrographic seizures are deleterious for traumatic brain injury patients" and their suggestion "that seizures can potentiate the metabolic distress of the brain injured patient and hence may lead to permanent cellular injury" are both justified and important. In addition to further studies to confirm and expand upon this one, a logical next step would be to investigate whether intervening in a timely fashion can prevent these adverse physiologic effects and ultimately improve outcome.

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