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# Nonconvulsive electrographic seizures after traumatic brain injury result in a delayed, prolonged increase in intracranial pressure and metabolic crisis

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## Abstract

**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).

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**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 hr 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. (Crit Care Med 2007; 35:)

## Keywords

continuous electroencephalography; intensive care; seizures; status epilepticus; nonconvulsive; traumatic brain injury; microdialysis; lactate; pyruvate; intracranial pressure

Intracranial pressure (ICP) remains one of the principal treatment targets for traumatic brain injury (TBI) (1). Elevation of ICP is due to brain edema, mass effect from hemorrhagic lesions, and possibly from disrupted pressure autoregulation. The treatments for ICP have been focused on these pathophysiologic mechanisms. While the treatment principals for elevated ICP have been codified into guidelines and practiced by many intensivists, ICP often remains refractory to treatment. Indeed, treatment failure resulting in herniation and death occurs frequently. The mechanisms for persistently elevated ICP have not been well elucidated, but candidate mechanisms include sustained hyperemia, excitotoxicity, and osmotic rebound. In contrast, little attention has been paid to the adverse effects of epileptic activity upon the extent or duration of elevated ICP after TBI.

In recent years, post-traumatic seizures have been documented to occur frequently after human TBI (2). Indeed, seizures are frequent after a variety of hemorrhagic injuries to the brain (3, 4). The incidence of seizures increases as a function of the severity of injury, and other selected features of the injury such as the presence of hemorrhagic contusions. Post-traumatic seizures previously have been associated with increased glycolysis in both animal and human metabolic imaging studies (5, 6) and have been associated with alterations of brain levels of glutamate and other excitatory amino acids (7). However, it is presently unclear whether post-traumatic seizures result in an increase in ICP or other adverse consequences for the patient. This has resulted in uncertainty about how aggressively to treat seizures, especially those that are nonconvulsive or purely electrographic.

It is in this context that we studied the cerebral hemodynamic and metabolic effects of electrographic post-traumatic seizures in a cohort of TBI patients monitored by continuous electroencephalograms (EEGs). The primary hypothesis was that nonconvulsive

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electrographic seizures result in an episodic increase in ICP. The secondary hypothesis was that electrographic seizures result in an increase in microdialysis lactate/pyruvate ratio (LPR). We utilized a within-subjects, before-after seizures design as well as a separate between-subjects cohort comparison design to test our hypotheses.

## METHODS

### Patient Selection

The study was approved by our medical institutional review board. Twenty consecutive patients were monitored by both continuous EEG (cEEG) and microdialysis for 3 yrs. Ten of these patients had seizures and were compared with 10 matched patients without seizures, based on age, computed tomography–assessed lesion, and initial Glasgow Coma Score.

### General Management Protocol

Our general management protocol has been published previously (2). ICP was kept below 20 mm Hg using a stepwise management strategy (i.e., cerebrospinal fluid drainage, hyperventilation to $PCO_2$ of 30–34, and hypertonic saline). Jugular venous oximetry was performed to monitor for jugular venous desaturation, and blood pressure was adjusted to keep the jugular venous oximetry between 60% and 70%. Cerebral perfusion pressure was kept >60 mm Hg using norepinephrine if needed. Core temperature from the jugular vein was used and kept between 37°C and 37.6°C through the use of medications (acetaminophen) and intravascular and surface cooling devices. All patients received phenytoin for at least 7 days. None of the patients studied received intravenous or oral steroids. In both groups, patients were maintained on intravenous crystalloids without glucose (normal saline with potassium chloride) for the initial 4 hrs after injury. Enteral nutrition (Isocal HN, Novartis, Basel, Switzerland) was provided via nasogastric tube at a rate of 1 mL/kg, with feedings adjusted for gastric residuals and caloric goals on an individual basis. Enteral feedings were started within 6 hrs after injury and were adjusted to maintain a caloric goal of 30 Cal/kg of adjusted ideal body weight. Audit of nutritional records indicates that this goal was met during the period of microdialysis observation. Intravenous sedation consisted of continuous propofol at a dose ranging from 10 to 50 μg/kg per min, with titration adjusted to maintain intracranial pressures <20 mm Hg or Ramsay scale score of 3.

### Continuous EEG Protocol

These methods have been described previously (2). EEG was continuously monitored at the patient's bedside starting immediately at admission to the intensive care unit (ICU). The cEEG was continuously displayed at the bedside, 24 hrs per day, for moment-to-moment on-line observation by physicians and nurses. A physician trained in interpretation of EEG reviewed the ongoing EEG activity at the bedside at least three times each day and additionally when the bedside nurse reported suspicious EEG activity. A 14-channel, 12-electrode montage was used employing the following electrode derivations: F4-CZ, T4-CZ, P4-CZ, O2-CZ, F3-CZ, T3-CZ, P3-CZ, O1-CZ, F4-T4, T4-P4, P4-O2, F3-T3, T3-P3, and P3-O1 (according to the 10–20 international system).

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Seizures were detected in one of three ways: on-line identification of seizures by the neuro-ICU nurse or neurointensivist, during the EEG screening by the neurointensivist, or by total power trend seizure detection method (previously described by Vespa and colleagues [2]). In brief, the EEG was converted in realtime using the Fast-Fourier method to several quantitative parameters once every minute, such as the total power of the EEG, and displayed at the bedside as a continuous linear histogram. A seizure resulted in an increase in the power and was detectable as a surge in the histogram, which could be detected easily by an inexperienced clinician. A bedside printed seizure-detection template was used by the nurses. The date and time of the seizure and the clinical behavior noted by the bedside neuro-ICU nurse or neurointensivist were recorded. Each seizure was confirmed by an independent physician blinded to the clinical condition (PMV or CM). Seizure type was characterized as focal, hemispheric, or generalized according to the EEG at time of onset. The durations of individual seizures were recorded along with the total (aggregate) duration of seizures during the ICU stay. Status epilepticus was defined as the persistence of discretely interrupted or continuous electrographic seizure spike-wave discharges for >10 mins.

### Microdialysis Methods

Cerebral microdialysis was performed using the CMA70 probe (10-cm flexible shaft, 10-mm membrane length, 20-kd cutoff; CMA, Stockholm, Sweden) inserted via a twist-drill burr hole adjacent to an existing ventriculostomy catheter or in pericontusional tissue at the time of surgery. The probe location was confirmed on computerized tomographic or magnetic resonance imaging of the brain with the microdialysis probe in place and was designated to be in normal-appearing white matter. Site location was confirmed by magnetic resonance fluid attenuation inversion recovery sequence imaging performed on a 1.5 T imaging device (Sonata, Siemens, Germany). The microdialysis catheter was inserted to a depth of 1.5–2 cm below the skin at an angle of 30 degrees lateral to the trajectory of the ventriculostomy, to place the catheter into the white matter. The probe was tunneled 3 cm under the skin and secured to the scalp with a flat profile, and then attached to the perfusion pump. Normal saline was perfused through the catheter at a rate of 1 μL/min, and fluid was collected in 60-min samples and placed in dry ice or directly into the CMA 600 microdialysis analyser (CMA) for analysis. The initial 60-min sample was not used for analysis because this was the time allowed for stabilization of the probe. Microdialysis was not interrupted for transport or bedside testing.

Frozen samples were briefly centrifuged and then analyzed on the CMA 600 in batch analysis. The standard CMA6 00 reagents were used for analysis. The hourly samples were run twice each for each analyte, and the mean final value was used. Quality control measurements using normal saline and water blank samples, as well as standardized solutions across a range of concentrations mimicking those of the human samples, were run weekly with an additional control sample for each subject. In all, 1,420 hourly samples for each of the seizure and nonseizure patients were reviewed.

The bedside nurse and research team maintained a detailed patient log to identify important events and to record times of vial sampling. In addition, automated computerized capture of

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all physiologic monitoring data was conducted using the University of California Los Angeles–derived Brain Injury Research Center database. The following data were recorded hourly: ICP, mean arterial blood pressure, cerebral perfusion pressure, heart rate, arterial oxygen saturation, core temperature, jugular venous oxygen saturation, EEG, and Glasgow Coma Score. The hourly administration of midazolam and propofol was recorded in both the seizure and nonseizure groups. The seizure group was found to have similar average daily dose and cumulative dose of midazolam and/or propofol before seizure onset as compared with the nonseizure group.

### Data Analysis

Data acquisition was performed using Office 2003 (Microsoft, Redmond, WA), while statistical procedures were conducted with R version 2.2.1 (University of Auckland, New Zealand). Univariate analyses were performed for the main variables comparing the seizure and nonseizure groups using analysis of variance and mixed effects model statistics as necessary.

## RESULTS

Twenty patients with severe TBI were studied by cEEG and cerebral microdialysis for 7 days after injury. Ten patients had electrographic seizures and ten patients were selected from a cohort of 50 similarly monitored patients based on age, Glasgow Coma Score, and computerized tomographic lesion matching. All patients had nonpenetrating head injury. Table 1 outlines the comparison between these two groups. The two groups were matched with respect to the types of brain lesions seen on computerized tomography, the Glasgow Coma Score, and the occurrence of surgery. Both groups had therapeutic levels of phenytoin but the seizure group did have higher mean phenytoin levels. Neither mortality nor Glasgow Outcome Score was statistically different between the two groups.

### Seizure Characteristics

The mean time of seizures was at 85 ± 7 hrs postinjury. However, there was a bimodal distribution of the timing of seizures, with an early peak seizure period, at 29 ± 14 hrs, and the later peak seizure period occurring at a mean of 140 ± 15 hrs after injury. There were multiple seizures per patient. All seizures were nonconvulsive with no apparent motor signs of seizures. Seven patients were categorized as having status epilepticus, because they demonstrated discrete seizures plus waxing–waning periodic epileptiform discharges lasting greater than 10 mins. The mean duration of an individual seizure was 2.8 ± 1.2 mins. The duration of status epilepticus before seizure abolition was 41 ± 7.5 mins. The remaining three patients had only discrete seizures. The seizures frequently were clustered and occurred over a several hour period before stopping. Four patients had seizures at the early peak time, four had seizures at the late peak time, and two had seizures at both peak times (Table 2).

As previously reported, the seizures were focal in origin with secondary generalization in 78% of cases. The seven patients with status epilepticus had secondarily generalized electrographic patterns with persistent waxing and waning periodic epileptiform discharges

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with variable repetition rates. The remaining three patients with discrete seizures had focal electrographic seizures with secondary generalization.

### Intracranial Pressure

Using a between-subjects design, we compared ICP between the seizure patients and the control patients. The mean ICP during the initial 168 hrs after TBI was higher in the seizure group compared with the nonseizure group (17.6 ± 6.5 vs. 12.2 ± 4.2 mm Hg; $p < .001$). The percentage time of ICP >20 mm Hg was greater in the seizure group compared with the nonseizure group (32 ± 28% vs. 6 ± 8.4%; $p < .02$) (Table 1). The time course of ICP in the seizure group demonstrated an increase in the mean ICP during the early and later windows of peak seizure activity (postinjury hrs 29 and 140). The seizure group had a secondary rise in mean ICP after 100 hrs, which was not seen in the nonseizure group (Fig. 1). After postinjury hr 100, the percentage time of ICP >20 mm Hg was greater in the seizure group compared with the control group (27 ± 27% vs. 5 ± 8%; $p < .04$) (Fig. 2).

Using a within-subjects design, we compared the behavior of ICP during the seizure for each patient, using mean ICP in the 12 hrs preceding the seizure (interictal ICP) and the 12 hrs starting at the onset of the seizure activity (ictal ICP). The ictal mean ICP was higher than the interictal mean ICP (22.4 ± 7 vs. 9.6 ± 5; $p < .002$) (Table 3). The percentage time of elevated ICP was >20 mm Hg during the ictal period compared with the interictal period (53 ± 33% vs. 7.5 ± 11%; $p < .001$). We explored whether different seizure types or duration were associated with various magnitudes of ICP elevation. We did not find that seizure duration or type correlated specifically with the magnitude of ICP elevation. In addition, patients with status epilepticus had mean increase in ICP similar to those with intermittent seizures (12 ± 4.5 vs. 13 ± 4.3 mm Hg; $p > .7$). Table 3 has a summary of the changes in ICP and LPR during the seizure.

### Microdialysis LPR

Using a similar between-subjects analysis paradigm as outlined for ICP, we examined the effect of seizures on the microdialysis LPR. In comparison with nonseizure patients, patients with seizures demonstrated higher mean LPR during the initial 168 hrs (35 ± 27 vs. 12 ± 10; $p < .04$). The percent time of LPR >40 was higher in the seizure compared with the nonseizure group (35 ± 27 vs. 11 ± 11; $p < .02$). The percent time of LPR <40 after postinjury hr 110 displayed a tendency to be higher in the seizure group compared with the nonseizure group (29 ± 33 vs. 9 ± 12; $p = .1$) (Fig. 2).

Using a within-subjects design, with a similar 12-hr baseline preceding the seizure (interictal) compared with the 12-hr mean starting at the time of the seizure, the mean ictal LPR value was higher than the interictal LPR (49.4 ± 16 vs. 23.8 ± 7.6; $p < .001$). The percentage time of elevated LPR >40 during the ictal periods was higher compared with the interictal periods (35 ± 27% vs. 16 ± 30%; $p < .03$). Similarly, the ictal mean glutamate level was higher compared with the interictal glutamate level in the seizure group (13.1 ± 20 vs. 2.6 ± 3.2; $p < .001$).

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### Treatment of Seizures

All patients were given phenytoin 300 mg once per day, with supplemental boluses if the trough phenytoin level was <10 mg/dL for at least 7 days. The seizure group had a higher mean phenytoin level compared with the nonseizure group (16.7 ± 9.5 vs. 11.1 ± 2.8 mg/dL). However, the nonseizure group experienced more frequent subtherapeutic trough phenytoin levels than the seizure group (21/70 daily levels <10 mg/dL in the nonseizure group vs. 8/70 in the seizure group). Once seizures were identified, lorazepam or midazolam was administered in bolus dose and a phenytoin bolus of 500 mg was administered. In the seven patients with status epilepticus, continuous infusions of midazolam (3) and pentobarbital (3) or propofol (1) were used to control seizures. In each case, the continuous infusions were titrated to achieve suppression of seizure activity, which uniformly required induction of a burst suppression pattern on the EEG. In all seven of these patients, levtiracetam was added at 3000–4000 mg per day divided into two doses.

## DISCUSSION

The principal results of this article are that: a) electrographic post-traumatic seizures are associated with an episodic increase in ICP; b) patients with post-traumatic seizures experience a higher mean ICP, a greater percentage of time of elevated ICP, and a more prolonged elevation of ICP beyond postinjury hr 100 as compared with nonseizure TBI patients; c) microdialysis LPR increases episodically during the seizure activity as compared with the interictal baseline; and d) LPR is elevated for a longer period of time and more often in patients with electrographic seizures compared with matched nonseizure TBI patients. These results are important because they confirm a long-held, but previously unsupported, premise that electrographic seizures are deleterious for TBI patients.

### Incidence of Post-Traumatic Seizures

The incidence of post-traumatic seizures has been debated over the past decade. Previous studies have documented the incidence of early post-traumatic seizures ranging between 2.8% and 15% (8–11). These studies used clinical seizure activity as the primary end point and did not use cEEG monitoring to define seizures. In addition, the primary focus of these studies was seizures that were witnessed immediately after the onset of trauma, often at the scene of the trauma. In contrast, we reported a 22% incidence rate of seizures when detailed, prospective cEEG monitoring of TBI patients in the ICU was used (2). Since that early seminal report of the use of cEEG to detect seizures in comatose brain injured patients, we and others have reported a consistently high incidence of electrographic seizures in patients with brain injury resulting from intracerebral hemorrhage (4), subarachnoid hemorrhage (3), and other acute injuries (12). In most studies, the incidence of electrographic seizures without any clinical motor signs of seizures, termed nonconvulsive seizures, accounts for >50% of seizures in the ICU and can only be detected by cEEG. The occurrence of prolonged status epilepticus after trauma is associated with an increased mortality rate and suggests a potential interaction between seizures and mortality after injury. Given these reports, cEEG is becoming more commonly used in neurointensive care units and treatment paradigms are being developed to focus on seizure suppression. These treatment paradigms

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include the use of cEEG and continuous infusions of midazolam, propofol, or pentobarbital to prevent all seizure activity.

In the current patient series, the electrographic seizures were exclusively non-convulsive. Hence, the response of elevated ICP did not seem to be related to motor activity of the patient or any presumptive effects of motor activity on ICP. Second, the seizures in this series were frequently repetitive and in most cases constituted status epilepticus. In many cases, the seizures consisted of waxing and waning bursts of evolving spike-wave discharges with momentary postseizure suppression of the background rhythm. This type of seizure activity has been described previously in our work (2) and that of others (3). This surface EEG activity most likely underestimates the duration and extent of seizure activity, and recent studies using electrocorticography to measure electrical activity on the brain tissue suggest more frequent seizure discharges after traumatic injury (13) in pericontusional tissue. Using surface electrodes, we found that most seizures in this cohort emanated from the frontal-temporal regions. These regions were uniformly injured in both the seizure and nonseizure group, with evidence of contusions. Therefore, our data agree with that of Dr. Parkin and colleagues (13) and suggest that the pericontusional regions are electrically active and capable of seizure activity. One could speculate that electrocorticography monitoring would detect even more frequent seizures than we reported here, but comparison studies have yet to be done.

### Potential Role of Electrographic Seizures on Brain Swelling and ICP

In the results reported above, we demonstrated that seizures were closely associated with an episodic increase in ICP. Our assessment of the data suggests that ICP goes up in response to seizures, and not vice versa. ICP during the period of seizure activity was higher than interictal periods in individuals. We attempted to determine whether there was a relationship between the duration of seizure activity and ICP, but our cases clustered around a somewhat uniform EEG behavior. The majority of the patients had frequent electrographic seizures and/or status epilepticus. Thus, the limited distribution of the data made it difficult to determine the effect of seizure duration on the intensity of ICP elevation. On average, the ICP nearly doubles with the occurrence of seizures, but we are not sure what minimal period of seizure activity is necessary to elicit an increase in ICP. This seizure activity was similar to that which we reported in our earlier article, but in this analysis we found that the seizure activity was prolonged and demonstrated waxing and waning activity that lasted for hours in several cases. This activity was associated with paroxysmal increases in ICP coincident with the seizure activity. This increase in ICP was not associated with clinical motor convulsions. We hypothesize that the increase in ICP was due to an increase in cerebral blood flow and blood volume associated with the electrical activity elicited by the seizure activity. Alternatively, the seizures may have resulted in an increase in extracellular edema and hence increased ICP. In the past, we reported increases in glutamate (14) and increased brain edema (15) with seizure activity after TBI and intracerebral hemorrhage, respectively. In the present series, we again demonstrated an increase in glutamate during the seizures. Thus, it is possible that seizures resulted in worsening brain edema and hence elevation in ICP.

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### Seizures Are Associated with Prolonged Metabolic Distress

The LPR has been a reliable and sensitive measure of brain metabolism across a wide spectrum of brain injury studies (16). The LPR has been demonstrated to reflect brain metabolism in injured patients. LPR is thought to represent alterations of mitochondrial function and redox state of the cell (16). LPR can increase with brain ischemia, under conditions of severely limited cerebral blood flow (2, 14, 17). We have demonstrated that LPR is elevated for 1 wk in previous studies (18). The elevation occurred in a majority of patients and correlated with poor outcome. In a combined positron emission tomography plus microdialysis study, we compared LPR to regional rates of oxidative and glucose metabolism (19). We determined that LPR correlate best with non-ischemic reductions in oxidative metabolism and increases in glucose utilization (19). On balance, the majority of LPR elevations that we have observed in TBI patients have not been due to brain ischemia, but rather metabolic distress. Thus the cause(s) of this metabolic distress and hence elevated LPR have remained poorly described to date.

In this study, we proposed to determine whether seizures could result in episodic increases in LPR. Using a within-subject design, we observed that LPR increased when electrographic seizures occurred. These results are similar to our previous findings of elevated microdialysis glutamate (7) and glycerol (8) with seizure activity. This elevation in LPR lasted for a variable period of time in the seizure patients, as reflected by the mean percentage time of LPR >40 ranging from 1% to 93% (Table 3). This suggests that seizures have a variable effect on the metabolic response in these patients. The sources of this variability may be related to the duration of ICP elevation, intersubject differences in the interictal metabolism state, the extent of seizure involvement by the tissue being sampled by microdialysis, or the duration of seizure activity. We have not been able to separate these variable effects, and it may be that one or more of these factors influenced our results. Ideally, we would have liked to have placed the microdialysis probe into the seizure focus to control for at least one of these variables, but this is impractical in most cases. Indeed, the seizure cohort demonstrated long-lasting elevations in LPR in comparison with the nonseizure cohort, suggesting that the seizure group was more prone to LPR elevation. Given that we prospectively matched patients based on injury severity, age, and injury types, we consider the possibility that the presence of seizures was influential in the prolonged elevation in LPR. However, given the small sample size, we recognize that our data are somewhat limited and that intrinsic patient differences partially could explain the prolonged elevation in LPR in the seizure group. Nonetheless, it does appear that LPR increases during seizures, which is evidence that post-traumatic electrographic seizures play an adverse role on brain metabolism. In experimental studies, anticonvulsants can worsen outcome after TBI (15), but in some models of brain injury the administration of anticonvulsants to stop post-traumatic seizures actually improves outcome (20). Given our within-subjects design and time-locked data, we do not think that administration of anticonvulsants elicited changes in glutamate or LPR. However, we agree that there is a need for the perfect anticonvulsant agent that not only stops seizures but is neuroprotective and does not cause adverse cognitive effects over the long term (2).

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## CONCLUSION

The present study has several potentially important implications. Namely, electrographic seizures can result in increased ICP, especially delayed increases in ICP beyond 96 hrs. This is important because the use of continuous EEG to detect seizures may result in improved ICP control, especially for patients with ICP that is refractory to conventional treatment measures. Second, our data suggests that these seizures are not benign epiphenomina but rather play a role in intracranial hemodynamics and hence could be harmful on this basis alone. Third, these data suggest that seizures can potentiate the metabolic distress of the brain injured patient and hence may lead to permanent cellular injury. Thus, identifying and stopping seizures has the potential to avoid this secondary metabolic distress and may in turn potentiate improved outcome. We have ongoing studies to determine whether there are long lasting effects of acute seizures on neurologic and anatomical outcome, which remain the gold standard. Thus, our data confirms our earlier findings and suggest that post-traumatic seizures are a significant therapeutic target for patients with traumatic brain injury.

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## REFERENCES

1. Vincent JL, Berre J. Primer on medical management of severe brain injury. Crit Care Med. 2005; 33:1392–1399. [PubMed: 15942361]
2. Vespa PM, Nuwer MR, Nenov V, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous EEG in the intensive care unit. J Neurosurg. 1999; 91:750–760. [PubMed: 10541231]
3. Claassen J, Mayer SA, Kowalski RG, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004; 62:1743–1748. [PubMed: 15159471]
4. Vespa P, O'Phelan K, Mirabelli J, et al. Acute seizures after intracerebral hemorrhage: A factor in progressive midline shift and outcome. Neurology. 2003; 60:1441–1446. [PubMed: 12743228]
5. Bergsneider MA, Hovda DA, Shalmon E, et al. Cerebral hyperglycolysis following severe human traumatic brain injury: A positron emission tomography study. J Neurosurg. 1997; 86:241–251. [PubMed: 9010426]
6. Roncati Zanier E, Lee SM, Vespa PM, et al. Increased hippocampal CA3 vulnerability to low-level glutamate analogue following lateral fluid percussion injury. J Neurotrauma. 2003; 20:409–420. [PubMed: 12803974]
7. Vespa P, Prins M, Ronne-Engstrom E, et al. Increase in extracellular glutamate caused by reduced cerebral perfusion pressure and seizures after human traumatic brain injury: A microdialysis study. J Neurosurg. 1998; 89:971–982. [PubMed: 9833824]
8. Annegers JF, Grabow JD, Groover RV, et al. Seizures after head trauma: A population study. Neurology. 1980; 30:683–689. [PubMed: 7190235]
9. Jennet WB, Lewin W. Traumatic epilepsy after closed head injuries. J Neurol Neurosurg Psychiatry. 1980; 23:295–301.
10. Lee ST, Wong CW, Yeh YS, et al. Early seizures after moderate closed head injury. Acta Neurochir. 1995; 137:151–154. [PubMed: 8789655]
11. Temkin NR. Prophylactic anticonvulsants after neurosurgery. Epilepsy Curr. 2002; 2:105–107. [PubMed: 15309132]
12. Vespa P. EEG for the detection of seizures in traumatic brain injury, infarction, and intracerebral hemorrhage: "To detect and protect.". J Clin Neurophysiol. 2005; 20:99–106. [PubMed: 15805809]

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13. Parkin M, Hopwood S, Jones DA, et al. Dynamic changes in brain glucose and lactate in pericontusional areas of the human cerebral cortex, monitored with rapid sampling on-line microdialysis: Relationship with depolarisation-like events. J Cereb Blood Flow Metab. 2005; 25:402–413. [PubMed: 15703701]
14. Enblad P, Valtysson J, Andersson J, et al. Simultaneous intracerebral microdialysis and positron emission tomography in the detection of ischemia in patients with subarachnoid hemorrhage. J Cereb Blood Flow Metab. 1996; 16:637–644. [PubMed: 8964803]
15. Hoover RC, Motta M, Davis J, et al. Differential effects of the anticonvulsant topiramate on neurobehavioral and histological outcomes following traumatic brain injury in rats. J Neurotrauma. 2004; 21:501–512. [PubMed: 15165359]
16. Hillered L, Vespa PM, Hovda DA. Translational neurochemical research in acute human brain injury: The current status and potential future for cerebral microdialysis. J Neurotrauma. 2005; 22:3–41. [PubMed: 15665601]
17. Enblad P, Frykholm P, Valtysson J, et al. Middle cerebral artery occlusion and reperfusion in primates monitored by microdialysis and sequential positron emission tomography. Stroke. 2001; 32:1574–1580. [PubMed: 11441204]
18. Vespa P, McArthur D, Glenn T, et al. Persistently reduced levels of extracellular glucose early after traumatic brain injury correlate with poor outcome at six months: A microdialysis study. J Cereb Blood Flow Metab. 2003; 23:865–877. [PubMed: 12843790]
19. Vespa P, Bergsneider M, Hattori N, et al. Metabolic crisis without brain ischemia is common after traumatic brain injury: A combined microdialysis and positron emission tomography study. J Cereb Blood Flow Metab. 2005; 25:763–774. [PubMed: 15716852]
20. Williams AJ, Tortella FC, Lu XM, et al. Antiepileptic drug treatment of nonconvulsive seizures induced by experimental focal brain ischemia. J Pharmacol Exp Ther. 2004; 311:220–227. [PubMed: 15140918]

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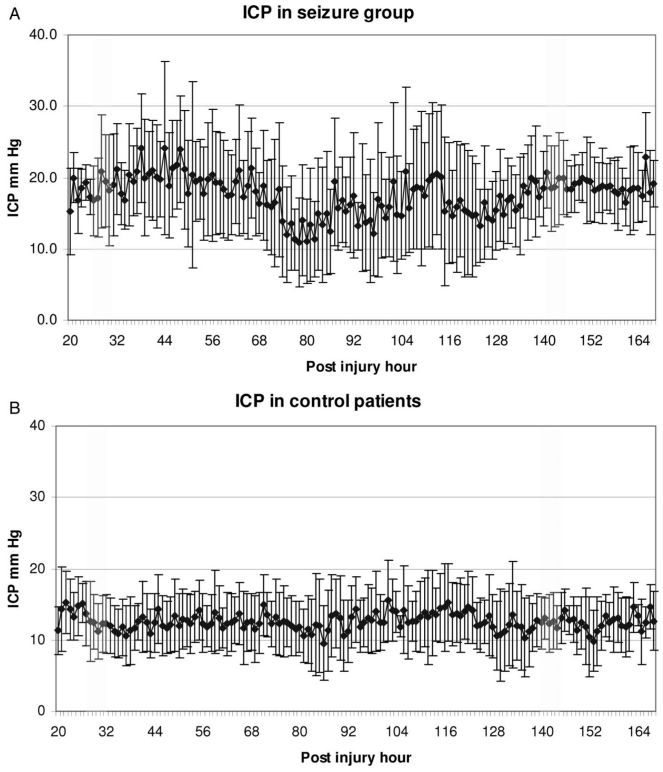


**Figure 1.**

Comparison of intracranial pressure (*ICP*) between groups: *A*, the mean ICP of all ten seizure patients by postinjury hour. *B*, the mean ICP of all ten patients in the comparison nonseizure group. The time course of ICP is shown. Note the higher ICP overall, and the persistence of elevated ICP beyond postinjury hr 100. The *yellow bars* denote the window of time during which the peak incidence of seizures occurred during the early and late phase. Of note is that the mean ICP continues to be elevated after hr 140 in the seizure group, whereas the ICP is lower in the nonseizure group.

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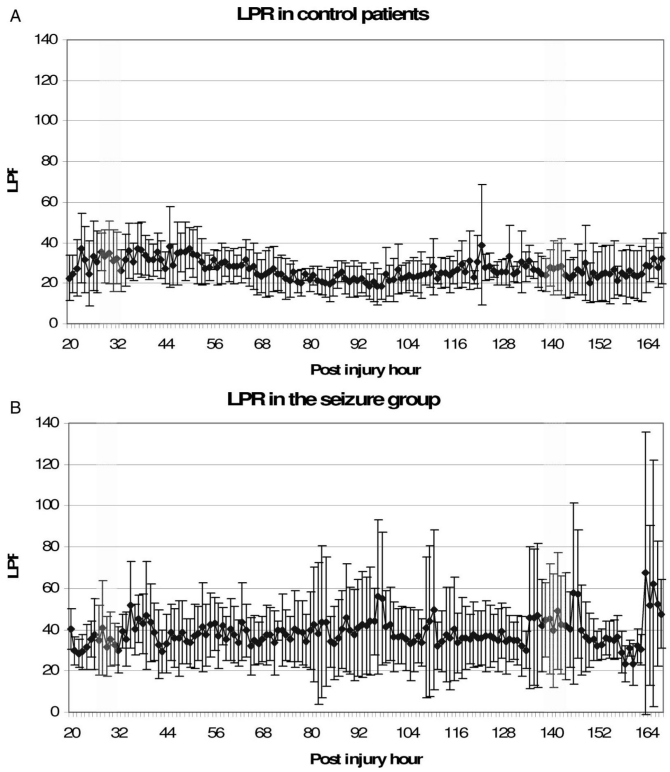


**Figure 2.**

Comparison of lactate/pyruvate ratio (*LPR*) between groups: *A*, the mean LPR of all ten seizure patients by postinjury hour. *B*, the mean LPR of all ten patients in the comparison nonseizure group. The seizure group displays higher LPR overall, and the persistence of elevated LPR beyond postinjury hr 100. The *yellow bars* denote the window of time during which the peak incidence of seizures occurred during the early and late phase. Of note is that the mean LPR is >40 at hr 140 in the seizure group but not in the nonseizure group.

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**Table 1**

Patient characteristics

| Clinical Parameter | Seizure Group | Nonseizure Group | *p* Value |
|---|---|---|---|
| Age | 49.7 ± 16 | 49.2 ± 16 | .94 |
| Glasgow Coma Scale score | 7.9 ± 3.1 | 7.6 ± 1.8 | .56 |
| CT lesions | | | .8 |
| Contusions | 6 | 5 | |
| Contusions + SDH | 2 | 3 | |
| Contusions + DAI | 2 | 2 | |
| Mean ICP | 17.6 ± 6.5 | 12.2 ± 4.2 | .001 |
| Mean LPR | 38.6 ± 18 | 27 ± 9 | .001 |
| % Time ICP >20 | 32 ± 28 | 6 ± 8 | .02 |
| % Time LPR >40 | 35 ± 27 | 12 ± 10 | .04 |
| Surgery | 4/10 | 6/10 | N/A |
| Phenytoin levels | 11.1 ± 3.4 | 16.7 ± 9.3 | .03 |
| GOS | 2.4 ± 0.7 | 2.3 ± 0.8 | .92 |
| Death | 1/10 | 2/10 | N/A |

SDH, subdural hemorrhage; DAI, diffuse axonal injury; ICP, intracranial pressure; LPR, lactate/pyruvate ratio; GOS, Glasgow Outcome Score.

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## Table 2

Seizure data

| Patient | Type | Seizure Focus | No. of Seizures | Day | Duration (mins) |
|---|---|---|---|---|---|
| 1 | Focal, NC | RFT | Status | 6 | 2 |
| 2 | Focal, NC | RFT | Status | 6 | 2 |
| 3 | Focal, NC | LFT | Status | 1 | 6 |
| 4 | Focal, NC | RFT | Status | 1 | 3 |
| 5 | Focal, NC | LFT | 3 | 6 | 2 |
| 6 | Focal, NC | LTP | 4 | 2 | 2 |
| 7 | Focal, NC | LFT | Status | 2 | 3 |
| 8 | 2nd gen | LTP | Status | 2 | 3 |
| 9 | 2nd gen | RFT | Status | 2 | 2 |
| 10 | Focal, NC | RFT | 2 | 5 | 3 |

NC, nonconvulsive; R, right; FT, frontal temporal; Status, status epilepticus; L, left; TP, temporal pole; 2nd, secondary generalization.

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**Table 3**

Intracranial pressure (ICP) before and after seizure

| Patient | Interictal ICP | Ictal ICP | Delta ICP with Seizure | Interictal LPR | Ictal LPR | Ictal % LPR >40 |
|---|---|---|---|---|---|---|
| 1 | 12 | 25 | 13 | 38 | 50 | 18 |
| 2 | 17 | 35 | 18 | 20 | 35 | 62 |
| 3 | 6 | 25 | 19 | 20 | 60 | 23 |
| 4 | 14 | 22 | 8 | 18 | 33 | 1 |
| 5 | 8 | 25 | 17 | 18 | 25 | 9 |
| 6 | 16 | 25 | 10 | 18 | 41 | 36 |
| 7 | 6 | 18 | 12 | 16 | 70 | 33 |
| 8 | 2 | 10 | 8 | 29 | 70 | 94 |
| 9 | 5 | 14 | 8 | 29 | 60 | 36 |
| 10 | 10 | 25 | 15 | 32 | 50 | 38 |
| Ave ± SD | 9.6 ± 5 | 22.4 ± 7 | 12.8 ± 4.3 | 23.8 ± 7.6 | 49.4 ± 16 | 35 ± 27 |

LPR, lactate/pyruvate ratio; Ave, average.