Seizures

69

Elisabeth Ronne-Engström and Jon Axel Forsse

Recommendations

Level I

There are insufficient data to support a Level I recommendation regarding either treatment for early posttraumatic seizures (PTS) or anti-seizure prophylaxis after head trauma.

Level II

Early posttraumatic seizures should be treated. Anticonvulsants may be used to decrease the incidence of early PTS (within 7 days of injury).

Level III

When seizures occur, it is important to re-evaluate the clinical situation with respect to intracranial lesions requiring surgical intervention. Prophylactic anti-seizure therapy may be considered as a treatment option to prevent early PTS in young paediatric patients and infants at high risk for seizures following head injury.

E. Ronne-Engström (✉)
Department of Neuroscience, Neurosurgery, Uppsala University, Uppsala, Sweden
e-mail: elisabeth.ronne.engstrom@akademiska.se

J. A. Forsse
Department of Neurosurgery, Odense University Hospital, Odense, Denmark
e-mail: jon.axel.forsse@rsyd.dk

69.1 Overview

There are no randomised, controlled, double-blind studies regarding treatment of early seizures after TBI, but observational studies support that seizures should be treated as soon as they occur. The basic idea of neurointensive care of TBI is to identify and treat conditions that compromise the brain's supply and use of oxygen and glucose. Seizure activity in the acute phase impairs this in a number of ways and can therefore worsen the brain injury. Neuronal firing causes a massive release of the potentially neurotoxic transmitter glutamate (GLU). In order to clear the synaptic space from GLU, there is an efficient glial uptake; however, it is highly energy dependent. Seizures increase energy demand, which can cause an energy failure in the brain developing into manifest ischaemia. Seizure activity can also cause significant changes in cerebral blood flow, with both increases and decreases observed.

It is debated whether anticonvulsant prophylaxis after head trauma should be used or not. The Brain Trauma Foundation states in its latest review that an adequate treatment with phenytoin or levetiracetam reduces the incidence of early seizures, but that evidence of effect on outcome is lacking (Carney et al. 2017). A major confounding factor is that earlier studies based their conclusions only on clinically observable seizures. The Brain Trauma Foundation states that further studies are needed and that such studies should

T. Sundstrøm et al. (eds.), *Management of Severe Traumatic Brain Injury*,
https://doi.org/10.1007/978-3-030-39383-0_69

use continuous EEG (cEEG) monitoring to identify seizures. Once seizures occur, they could either be a result of the original trauma or an indication that new intracranial lesions have developed. Treatment of repeated seizures and status epilepticus is a matter for qualified neurointensive care, multimodality monitoring and a team approach including neurosurgeons, neurologists, neurophysiologists and neurointensivists.

69.1.1 Background

Seizures occurring after traumatic brain injury (TBI) are usually described as either early (within first week after trauma) or late (thereafter). These are two qualitatively different phenomena, probably to some extent with separate pathophysiological mechanisms. The true incidence of early seizures is presently discussed. Based on clinical observations, the incidence was estimated to ~10%. However, continuous EEG monitoring shows that early seizures are more common and are seen in up to 50% of TBI patients who are admitted to neurointensive care. Early seizures are more often seen in younger children and the elderly and in those with subdural/epidural haematomas (alone or in combination with brain contusions) (Bennett et al. 2017; Arndt et al. 2016; Vespa et al. 1999; Ronne-Engstrom and Winkler 2006).

Late seizures manifest as posttraumatic epilepsy and develop in approximately 5% of TBI. Posttraumatic epilepsy accounts for 20% of symptomatic epilepsy in the population (Lowenstein 2009) and is more common after penetrating injury, severe closed injury, focal lesions and age >65 (Pohlmann-Eden and Bruckmeir 1997; Annegers and Coan 2000).

Early seizures are also believed to be a risk factor for posttraumatic epilepsy, and there seems to be a time window for therapeutic intervention before the traumatic brain scar matures into a chronic epileptic region.

There are two main indications for monitoring and treatment of seizures after head trauma: to avoid worsening of traumatic brain injuries in the acute phase and to avoid fatal status epilepticus.

69.1.2 The Relation of Seizures to the Acute Brain Injury

There are several mechanisms by which seizure activity in the acute phase can exacerbate the brain trauma. Neuronal firing causes a massive release of the potentially neurotoxic transmitter glutamate (GLU). Extracellular GLU release during seizure activity has been demonstrated with intracerebral microdialysis in patients with chronic epilepsy (During and Spencer 1993; Ronne-Engstrom et al. 1992) and in TBI patients (Vespa et al. 1998). Another problem is that the postsynaptic glial uptake of GLU is highly energy dependent (Magistretti and Pellerin 1999). Seizure activity can thus cause a significant increase in the energy demand. In the acute phase after trauma, with an already strained brain metabolism, an increased energy demand can result in manifest ischaemia due to energy failure with demands higher than availability (Samuelsson et al. 2007). Seizure activity can also cause significant changes in cerebral blood flow (CBF). This has been demonstrated with several techniques, e.g. cortical blood flow measurements using laser Doppler fibre attached to subdural strip electrodes (Ronne-Engstrom et al. 1993). Increased as well as decreased CBF was detected during seizures, and both these situations are potentially harmful. Increased CBF can increase ICP by vasodilatation, and a decreased CBF can worsen an energy failure situation. The blood flow changes are probably coupled with dynamic changes in metabolic demands. Vespa showed that patients with TBI and repetitive nonconvulsive seizures had both higher mean ICP and higher lactate/pyruvate ratio measured with intracerebral microdialysis, marking perturbed energy metabolism (Vespa et al. 2007).

69.2 NICU Management

69.2.1 Seizure Monitoring

The general idea with NICU monitoring is to identify and treat conditions that compromise the oxygen and glucose supply to the brain or increase metabolic demands, e.g. fever and epileptic sei-

zures. As EEG patterns depend on the integrity of the brain structures as well as on the cerebral blood flow and metabolism, continuous EEG is theoretically an ideal monitoring modality. EEG is in fact so far the only available method for online real-time monitoring of the brain's functions. There are still problems with the technique, such as the availability of EEG reading on a 24-h basis. However, since EEG today is done digitally, computerised treatment of the EEG signal can facilitate the EEG reading. An example of this is the use of the trends of the EEG's total power (Vespa 2005). High values can indicate seizure activity, and when this is found, raw EEG during this time period is studied. Another advantage of digital EEG is that it allows for web-based reading.

69.2.2 Prophylaxis

It is debated whether anticonvulsant prophylaxis should be used or not. A major confounding factor when reading the literature is that early studies base their conclusions only on clinically observable seizures. The Brain Trauma Foundation has in their guidelines for treatment of TBI also reviewed the scientific basis for anti-seizure prophylaxis (Carney et al. 2017). Their conclusion is that there is evidence that an adequate treatment with phenytoin reduces the incidence of early seizures, but not that of posttraumatic epilepsy. Valproate may have a comparable effect but may also be associated with a higher mortality. They also state that more studies are needed on the effect on outcome by reducing early seizures and that such studies should use continuous EEG monitoring to identify seizures. Using drugs with anticonvulsant properties, e.g. midazolam, in sedating intubated patients could be an alternative to anti-seizure prophylaxis. No seizures were monitored in a study were most of the patients were sedated with thiopental and midazolam (Olivecrona et al. 2009).

69.2.3 Treatment of Seizures

When seizures occur, it is important to re-evaluate the clinical situation to see if something has changed. This could be the development of a brain contusion, subdural haematoma or a cortical venous thrombosis. One should also keep in mind the possibility of withdrawal symptoms for alcohol/drug addicts with TBI. Early posttraumatic seizures should be treated as soon as they occur, which is easier if the unit has a protocolled treatment. The suggested treatments below are from the Uppsala University Hospital treatment program for seizures in neurointensive care. *Single seizures* could be treated with diazepam 10 mg i.v. or lorazepam 2–4 mg i.v. Secondary prophylaxis with phenytoin or levetiracetam should be considered.

In case of *repeated seizures*, treatment as well as prophylaxis should be started. It is preferred that continuous EEG monitoring is used to ensure that the patient becomes seizure-free from the treatment. Respiration and cardiovascular functions should also be monitored, and the threshold for intubation and mechanical ventilation should be low. The choice of pharmacological substances should be based on local guidelines for sedation of intubated patients. Propofol infusion is often used. A bolus dose of 1–3 mg/kg is given, followed by 1–5 mg/kg/h. Treatment should not extend 48 h. Midazolam infusion is also efficient. Midazolam is administered with a bolus of 0.2 mg/kg i.v. followed by 0.1–0.5 mg/kg/h. To this is added phenytoin infusion, 15–20 mg FE/kg, followed by intermittent doses of 250 mg FE/kg × 3. It is important that adequate serum concentrations are achieved and daily checks are advised. Levetiracetam can be used at this stage as an alternative to phenytoin and may have a preferable adverse event profile (initial dose 500 mg × 2 daily, oral or i.v. with loading dose 30–70 mg/kg max 3 g considered safe).

If seizures still are present, lorazepam, levetiracetam, lamotrigine, carbamazepine or valproate can be added. Anticonvulsant drugs have many side effects including interaction with other drugs, skin reactions, deranged liver function and haematologic disturbances, such as clotting disturbances, which can be especially serious for TBI patients.

Status epilepticus that does not resolve with the treatment above can be treated with thiopental infusion. Bolus dose is 100–250 mg and is followed by 50 mg every 2–3 min until EEG is low voltage without seizure activity or burst suppression. This is followed by an infusion of 3–5 mg/kg/h. There should be at least a period of 12–24 h free from seizures before the treatment stops. The patient with thiopental treatment must be on mechanical ventilation with a strict control on electrolytes, temperature and vital organ functions.

69.3 Specific Paediatric Concerns

There are only a few studies in the literature regarding children and early posttraumatic seizures. In one study, 7% had immediate seizures (Emanuelson and Uvebrant 2009). This contrasts to a study showing that as much as 68% of children with moderate and severe TBI developed early posttraumatic seizures. The two groups probably represent different severities of TBI (Liesemer et al. 2011). In a large retrospective cohort study from 2017, Bennet et al. concluded that posttraumatic seizures were diagnosed in 25.2% of children with severe TBI (Bennett et al. 2017).

The Brain Trauma Foundation guidelines state that prophylactic use of anti-seizure therapy is not recommended for children with severe traumatic brain injury (TBI) for preventing *late* posttraumatic seizures (Level II) (Kochanek et al. 2012). However, it may be considered a treatment option in young paediatric patients and infants at high risk, for the prevention of *early* seizures (Level III).

Treatment of seizures and status epilepticus in children should follow similar strategies as in adults. However, the doses and choices of drugs should be carefully considered after the individual circumstances. For example, propofol is only recommended for starting sedation of children >1 month of age and should not be used for continuous sedation >24 h (Kaye et al. 2017). Continuous EEG monitoring can be very valuable in paediatric patients.

Tips, Tricks, and Pitfalls

- When seizures occur, exclude development of new intracranial lesions needing surgical intervention.
- Remember possible withdrawal symptoms for alcohol/drug addicts with TBI.
- *Treatment of single seizures*:
  - Intravenous diazepam 10 mg or lorazepam 2–4 mg.
  - Consider prophylaxis with phenytoin.
- *Treatment of repeated seizures*:
  - Start continuous treatment as well as prophylaxis.
  - Monitor vital functions and EEG.
  - Low threshold for intubation and artificial ventilation to enable more intense treatment.
  - Propofol infusion is commonly used. A bolus dose of 1–3 mg/kg is followed by infusion of 1.0–7.5 mg/kg/h until seizure activity is relieved. Midazolam can also be used, combined with propofol or as monotherapy, and starts with a bolus of 0.2 mg/kg i.v. followed by infusion of 0.1–0.5 mg/kg/h.
  - Phenytoin is added as prophylaxis with 15–20 mg FE/kg i.v. followed by 250 FE × 3. It is important that adequate serum concentrations are achieved, and daily checks are advised. Levetiracetam is considered a sufficient alternative to phenytoin.
  - If seizures persist, lorazepam, levetiracetam, lamotrigine, carbamazepine or valproate can be added.
- *Treatment of status epilepticus if not resolved with the treatment above*:
  - Thiopental infusion. Bolus dose is 100–250 mg and is followed by 50 mg every 2–3 min until EEG is low voltage without seizure activity or burst suppression. This is followed by an infusion of 3–5 mg/kg/h. There should be 12–24 h free from seizures before the treatment stops. Note: the patient must be on mechanical ventilation with strict control of electrolytes, temperature and vital organ functions.

References

Annegers JF, Coan SP. The risks of epilepsy after traumatic brain injury. Seizure. 2000;9(7):453–7.

Arndt DH, Goodkin HP, Giza CC. Early posttraumatic seizures in the pediatric population. J Child Neurol. 2016;31(1):46–56.

Bennett KS, DeWitt PE, Harlaar N, Bennett TD. Seizures in children with severe traumatic brain injury. Pediatr Crit Care Med. 2017;18(1):54–63.

Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ, Bratton SL, Chesnut R, Harris OA, Kissoon N, Rubiano AM, Shutter L, Tasker RC, Vavilala MS, Wilberger J, Wright DW, Ghajar J. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017;80(1):6–15.

During MJ, Spencer DD. Extracellular hippocampal glutamate and spontaneous seizure in the conscious human brain. Lancet. 1993;341(8861):1607–10.

Emanuelson I, Uvebrant P. Occurrence of epilepsy during the first 10 years after traumatic brain injury acquired in childhood up to the age of 18 years in the south western Swedish population-based series. Brain Inj. 2009;23(7):612–6.

Kaye AD, Fox CJ, Padnos IW, Ehrhardt KP, Diaz JH, Cornett EM, Chandler D, Sen S, Patil S. Pharmacologic considerations of anesthetic agents in pediatric patients: a comprehensive review. Anesthesiol Clin. 2017;35:e73–94.

Kochanek PM, Carney N, Adelson PD, Ashwal S, Bell MJ, Bratton S, Carson S, Chesnut RM, Ghajar J, Goldstein B, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents, second edition. Pediatr Crit Care Med. 2012;13(1):1–82.

Liesemer K, et al. Early post-traumatic seizures in moderate to severe pediatric traumatic brain injury: rates, risk factors, and clinical features. J Neurotrauma. 2011;28(5):755–62.

Lowenstein DH. Epilepsy after head injury: an overview. Epilepsia. 2009;50(Suppl 2):4–9.

Magistretti PJ, Pellerin L. Astrocytes couple synaptic activity to glucose utilization in the brain. News Physiol Sci. 1999;14:177–82.

Olivecrona M, et al. Absence of electroencephalographic seizure activity in patients treated for head injury with an intracranial pressure-targeted therapy. J Neurosurg. 2009;110(2):300–5.

Pohlmann-Eden B, Bruckmeir J. Predictors and dynamics of posttraumatic epilepsy. Acta Neurol Scand. 1997;95(5):257–62.

Ronne-Engstrom E, Winkler T. Continuous EEG monitoring in patients with traumatic brain injury reveals a high incidence of epileptiform activity. Acta Neurol Scand. 2006;114(1):47–53.

Ronne-Engstrom E, et al. Intracerebral microdialysis of extracellular amino acids in the human epileptic focus. J Cereb Blood Flow Metab. 1992;12(5):873–6.

Ronne-Engstrom E, Carlson H, Blom S, Flink R, Gazelius B, Spännare B, Hillered L. Monitoring of cortical blood flow in human epileptic foci using laser doppler flowmetry. J Epilepsy. 1993;6:145–51.

Samuelsson C, et al. Cerebral glutamine and glutamate levels in relation to compromised energy metabolism: a microdialysis study in subarachnoid hemorrhage patients. J Cereb Blood Flow Metab. 2007;27(7):1309–17.

Vespa P. Continuous EEG monitoring for the detection of seizures in traumatic brain injury, infarction, and intracerebral hemorrhage: "to detect and protect". J Clin Neurophysiol. 2005;22(2):99–106.

Vespa P, 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(6):971–82.

Vespa PM, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. J Neurosurg. 1999;91(5):750–60.

Vespa PM, et al. Nonconvulsive electrographic seizures after traumatic brain injury result in a delayed, prolonged increase in intracranial pressure and metabolic crisis. Crit Care Med. 2007;35(12):2830–6.