

Evidence-Based Medicine: Do Anti-Epileptic Drugs following Acute Brain Injury Prevent Seizures and/or affect Morbidity and Mortality?

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Abstract

The source for this systematic review abstract is: Schierhout G, Roberts I. [Anti-epileptic drugs for preventing seizures following acute traumatic brain injury](#). [Systematic Review] In: *Cochrane Database of Systematic Reviews* Issue 4. 2001.

MeSH words: Anticonvulsants, brain injuries, randomized controlled trials, seizures

Objective

To determine the effects of prophylactic anti-epileptic drugs for acute traumatic brain injury.

Search Strategy

The reviewers searched the Cochrane Injuries Group specialized register, MEDLINE and the registers of the Cochrane Stroke Group and Cochrane Epilepsy Group. Additionally, pharmaceutical companies who manufacture anti-epileptic medicines were contacted, the National Institute of Neurological Disorders and Stroke, Epilepsy Division, and the United States National Institute of Health.

Study Selection

Randomized Controlled trials of anti-seizure medications applied to study participants with clinically defined acute traumatic head injury of any severity. The review excluded trials that initiated anti-seizure agents more than eight weeks after the injury, studies that compared two different drugs or different doses of the same drug, and studies with unavailable data. The trial intervention was defined as anti-epileptic agents and included phenytoin, carbamazepine, and phenobarbital. Most of the trials excluded subjects who had a seizure prior to initiation of the anti-epileptic medication. The outcome measures were early seizures (within the first

week), late seizures (after the first week), death, severe disability or vegetative state and adverse reaction of skin rashes.

Data extraction

Two reviewers independently assessed all selected studies. Eligibility was determined by review of trial reports and correspondence with the trialists. The eligible trials were evaluated on quality of allocation concealment, drug type and drug dose. These three underlying differences were a priori hypothesized by the reviewers as potential causes of heterogeneity between trials. Relative risks and 95% confidence intervals were calculated for each trial on an intention to treat basis, which included pre-drug loading exclusions. Heterogeneity between trials was tested using a chi-squared test, where P less than or equal to 0.05 was taken to indicate significant heterogeneity. If statistical heterogeneity did NOT exist between trial data, then summary relative risks and 95% confidence intervals were calculated using a fixed effects model. Numbers needed to treat were calculated for seizure prevention and for non-fatal adverse effects.

Main results

The review consisted of six trials that included 1218 randomized patients.

Seizure Prevention

Early seizure prevention data was available from 4 of the 6 trials (890 patients) and there was no statistical heterogeneity. Therefore the reviewers calculated the pooled relative risk for early seizure prevention with treatment as **0.34** (95% CI 0.21, 0.54). The late seizure prevention data, with and without sensitive analysis demonstrate non significant relative risk {(0.92; 95% CI 0.69, 1.23), (1.28; 95% CI 0.90, 1.81) respectively}.

Death and Neurological Disability

Mortality data was available for 5 of the 6 studies (1054 patients). There was no statistical benefit of prophylactic anti-seizure treatment and mortality reduction with a pooled relative risk **1.15** (95%CI 0.89, 1.51).

Neurological disability based on the Glasgow Outcome Coma Scale was evaluated in 2 of the 6 trials. One study used carbamazepine and the

second phenytoin. Neither study showed a beneficial effect of prophylactic anti-seizures meds versus placebo regarding neurological disability (severe disability or vegetative state)

with RR of 1.49 (95% CI 1.06, 2.08) and 0.96 (95% CI 0.72, 1.39) in respective studies.

Skin Rashes

Only 2 of the 6 trials recorded the occurrence of skin rashes. Both reported an increase incidence of skin rashes in patients taking anti-seizure medications. The pooled relative risk was **1.57** (95%CI 0.90, 2.75)

Conclusions

There is no evidence that prophylactic anti-epileptics used at any time after head injury, reduce death and disability. There is evidence that prophylactic anti-epileptics reduce early seizures, but this is not supported by a reduction in late seizures. Insufficient evidence is available to establish the net benefit of treatment at any time after head injury. Future randomized placebo-controlled trials are needed.

Commentary: Clinical Implication

Each year an estimated 1.4 million people sustain a traumatic brain injury (TBI) in the United States. Of those, approximately 50,000 die and 260,000 are hospitalized. The estimated number of persons who become disabled each year from TBI is between 80,000 and 90,000. The U.S. Centers for Disease Control reports mean annual incidence rate for persons hospitalized with TBI and survived was 99 per 100,000. Hospitalization incidence rates are highest among persons 15-24 years of age and persons over age 65. [1]

The prevalence of TBI is estimated at 5.3 million U.S. citizens (2 percent of the population) living with disability as a result of a traumatic brain injury. Direct medical costs and indirect costs such as lost productivity of TBI totaled an estimated \$60 billion in the United States in 2000. [2]

Seizures in the immediate post-traumatic period after a head injury may cause secondary brain damage. Seizure activity causes increased metabolic demands, elevated intra-cranial

pressure, and increased neurotransmitter release. Patients with moderate to severe TBI are at high risk for additional injuries, including cervical spine fractures. The Pennsylvania Trauma Outcomes study reported a prevalence of

cervical spine injury among 41,142 cases of TBI was 8% [3]. One could postulate that tonic-clonic activity in a TBI patient with an undiagnosed cervical spine injury may increase the morbidity/mortality of their injury.

Posttraumatic epilepsy is a major source of morbidity after TBI, which complicates 20% to 25% of cases of severe head injury (Glasgow Coma Scale <9), and 5% to 10% of cases of mild to moderate injury (Glasgow Coma Scale 9-14). It is estimated that 5000 to 30,000 new cases of epilepsy each year result from TBI. Posttraumatic epilepsy is the most common cause of new-onset epilepsy in young adults. [4]

Anti-epileptic drugs can have a narrow therapeutic index. The most commonly cited drug in this review was phenytoin. Phenytoin has a myriad of well known adverse effects, some fatal. These include blood dyscrasias, neurologic impairment, and severe skin eruptions.

This systematic review attempts to answer the questions: Do anti-epileptic drugs prevent seizures following traumatic brain injury? And if so, does this affect death or disability (long term seizures) and at what potential adverse reactions to the drugs?

The review found that anti-epileptic drugs did decrease seizures in the first week after a TBI. However the pooled data did not show a reduction in overall mortality, persistent vegetative state or late seizures (Posttraumatic Epilepsy).

There was insufficient data to examine hematopoietic or neurologic adverse effects from the anti-seizure medications. However there was a trend to increased skin rashes as an adverse effect.

The net benefit of treating 100 patients following TBI with anti-seizure agents would be that ten would be kept seizure free in the acute phase and four may develop skin rashes.

Take-Home Message

Traumatic Brain Injury is common with potential for acute and long-term morbidity. Current evidence-based medicine supports using anti-seizure medications in the acute phase (most

likely initiated in the Emergency Department). This will reduce some acute phase seizures and possibly avoid worsened concomitant c-spine injuries. However long term reduction in seizures and mortality has not been shown. Future trials need to be conducted to determine if there is any net benefit of treatment.

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