EARLY SEIZURES AFTER TBI: TO TREAT OR NOT TO TREAT?
NO

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Traumatic brain injury (TBI) is a major cause of acquired epilepsy, and can exacerbate seizure severity in individuals with preexisting epilepsy. Posttraumatic epilepsy (PTE) accounts for approximately 20% of symptomatic epilepsy in the general population, and 5% of all patients seen at specialized epilepsy centers (Agrawal et al., 2006). PTE usually occur within 5 years of TBI, but the literature has described latent periods of up to 20 years.

The incidence of early posttraumatic seizures is 2-10% in most of the studies (Annegers et al., 1980; Annegers et al., 1998; Angeleri et al., 1999; Hahn et al., 1988. Epidemiologic studies have demonstrated a clear relationship between the severity of injury and the likelihood of developing seizures, with the higher risk in TBI cases associated with direct injury to brain parenchyma. Depressed skull fracture, intracerebral hematoma, and subdural hematoma have about a 25% risk of early (immediate or delayed) posttraumatic seizures. Depressed skull fracture, brain contusion, intracranial hemorrhage, coma duration, low Glasgow Coma Scale score, and older age are the high-risk factors for late seizures and PTE. (Annegers et al., 1998;Temkin , 2003)

The occurrence of seizures within the first week after TBI (‘‘early’’ seizures) are also a risk factor for the later development of epilepsy.

The mechanisms of post-traumatic seizures and epilepsy are not fully understood. In the experimental models, injury causes **both primary and secondary damage to the brain**. The epileptogenic process may start with an initial insult that may or may not involve acute seizure activity, but that lead to later development of epilepsy. The primary damage is caused by the impact itself, and it initiates ionic, molecular, and cellular alterations within seconds. This is followed by secondary damage that is composed of neurodegeneration, neurogenesis, astrocytosis, microgliosis, axonal and myelin injury, axonal sprouting, vascular damage, and angiogenesis (Reilly, 2001; Thompson et al., 2005; Pitkannen & McIntosh, 2006). Blood-brain barrier breakdown has often been documented in patients with TBI; animal studies have demonstrated that BBB breakdown is involved in the initiation of transcriptional changes in the neurovascular network that ultimately lead to delayed neuronal dysfunction and degeneration (Tomkins et al., 2011).

There is no evidence that any of the AEDs, when administered after TBI, would have any antiepileptogenic or disease modifying effects on the development of PTE in humans.

Five drugs (phenytoin, phenobarbital, carbamazepine, valproate, magnesium) have been tested for an antiepileptogenic effect, none has been shown to exert such an effect.

A significantly lower rate (RR 0.25) of early posttraumatic seizure development among the group treated with prophylactic AEDs (PHT) compared to the placebo group, was demonstrated (Temkin et al., 1990, class I study). The class II study evaluating carbamazepine also found a significantly lower rate of early seizures among the AED-treated group (RR 0.37). Glötzner et al., 1983). According to the AAN Report (Chang, Lowenstein, 2003) . Pooled class I studies **demonstrated a significantly lower risk of early post-traumatic seizures** (those occurring within 7 days after injury) in patients given phenytoin prophylaxis compared to controls (relative risk 0.37, 95% CI 0.18 to 0.74). However, pooled class I and class II studies demonstrated **no significant difference in the risk of late post-traumatic seizures** in patients given AED prophylaxis compared to controls (relative risk 1.05, 95% CI 0.82 to 1.35). Paradoxically, **three studies showed a higher incidence of PTE in patients receiving PHT or PB** than in untreated groups (Manaka,1992; Temkin et al.,1990; Young et al., 1983) .

Also, the prophylactic use of AEDs carries with it **the risk of adverse effects** that may be especially disabling in this population. In fact, in a number of studies adverse effects
were mild but fairly frequent, prompting medication change or discontinuation.

Another significant argument against routine treatment is related to the concern that AEDs, especially old ones (for instance, PHT and PB), **can potentially compromise the post - injury recovery**. In fact, as mentioned above, there is a number of deleterious mechanisms of the primary and secondary damage to the brain. The new AEDs might be more safe. However, until now only remacemide, topiramate, talampanel, lacosamide, and carisbamate have been investigated. No major harmful or beneficial effects have been reported. (Pitkanen et al, 2009).

Conclusions.

1. PHT and CBZ suppress early seizures, but none of the tested regimens show a positive effect on late. There is no evidence of antiepileptogenic or disease modifying effects of any of the AEDs.
2. The AED treatment with PHT and CBZ, known to prevent early seizures, is usually associated with a number of adverse effects, including the impact on cognition, that is especially undesired in TBI population.
3. These AEDS can potentially compromise the post - injury recovery.
4. Newer AEDs need to be evaluated in the laboratory and large clinical trials, as these agents employ different pharmacological mechanisms for seizure control. The drugs that stop the process of epileptogenesis may be different from those that suppress seizures.

Key references.

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