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POSTTRAUMATIC SEIZURES

Abstract: According to statistics, approximately 2% of all the head trauma patients, will develop post-traumatic seizures (PTS). About 20% of symptomatic epilepsy cases in the general population was caused by traumatic brain injuries (TBIs).

The risk of early and late PTS is dependent on the severity of the injury.

Administration of antiepileptics for seizure prophylaxis can reduce the early PTS but do not have effects on the late PTS. Routine seizure prophylaxis for the late PTS is not recommended.

Key words: *traumatic brain injury, seizures, prophylaxis*

INTRODUCTION

According to statistics, approximately 2% of all the head trauma patients, will develop post-traumatic seizures (PTS). However, the incidence is dependent on how severe injury has been. The PTS are observed in 12% of the severe TBI. (1, 2) There is a 5% to 7% incidence of having post-traumatic seizures (PTS) among all of the hospitalized TBI patients. (3) The TBI has been observed as the leading cause of epilepsy in adolescents. (3) About 20% of symptomatic epilepsy cases in the general population was caused by TBIs. (4)

Based on the time onset after the injury, posttraumatic seizures are divided into (5):

- early – occurring within 7 days,
- late – occurring after 7 days following the injury.

The risk of early and late PTS is dependent on the severity of the injury.

Traumatic brain injuries are divided into three categories based on the severity of injury (6):

- mild (loss of consciousness or amnesia lasting less than 30 minutes)
- moderate (skull fracture, loss of consciousness or post – traumatic amnesia for 30 minutes to 24 hours)

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– Severe (loss of consciousness or amnesia for more than 24 hours, intracranial hematoma, or brain contusion) 6.

Risk factors for developing PTS in patients with traumatic brain injury are: (7)

– Cortical contusion
– Subdural hematoma
– Epidural hematoma
– Intracerebral hematoma
– Penetrating head wound
– Glasgow Coma Scale (GCS) Score < 10
– Depressed skull fracture
– Seizure within 24 h of injury

The incidence of early PTS in severe head injury is high and account 30%. In mild to moderate brain injuries, the risk for early posttraumatic seizures is low and account approximately 1%. (6) In children with only a mild head injury, the incidence of early PTS is higher than in adults and accounts for 2.6%. (6) The children with early PTS are not at increased risk of developing late PTS, but repeated head injuries are risk factor for late PTS onset. (8)

The incidence of late PTS is 10–13% in a severe head injury in the first two year after the injury. (9) But, the incidence of PTS in a penetrating injury is much higher and accounts for 50% within fifteen years of the injury. (10)

Annegers et al. published in 1998 a big population study on 4541 patients with TBI, during the period from 1935 to 1984. They followed the incidence of PTS in this group and compared it to general population and found that the risk of PTS was related to the severity of TBI. (11)

The probability of seizures was in strong correlation to severity of TBI and accounted for: 0.7% in patients with mild brain injuries, 1.2% in moderate injuries and 10.0% in severe injuries within five years. (Figure 1.)

The standardized incidence ratio was also related to the severity of injury and accounted for 1.5 in mild, 2.9 in moderate and 17.0 in severe TBI. (Table 1.)

Duration of risk for PTS was also correlated to the severity of injuries. In patients with mild TBI there was an increased risk of PTS within five years after the injury. The risk of seizures in patients with moderate TBI was significantly increased in 10 years after the injury. In patients with severe TBI the risk of seizures was significantly elevated during the whole following period. (Table 2.)

Use of antiepileptic drugs in the patients already having the PTS is a standard practice. There was a strong controversy regarding the use of the antiepileptic drugs in antiseizure prophylaxis. Indications for the antiseizure prophylaxis, choice of drugs and duration of therapy vary widely among the clinicians.

In the acute period PTS may precipitate adverse events because of elevation of ICP, alterations in blood pressure and excess neurotransmitter release. (12) PTS could lead to accidental injuries, psychological disorders and work disability. On the other hand, drug administration could cause serious side effects such as allergic reactions, altered psychological reactions.

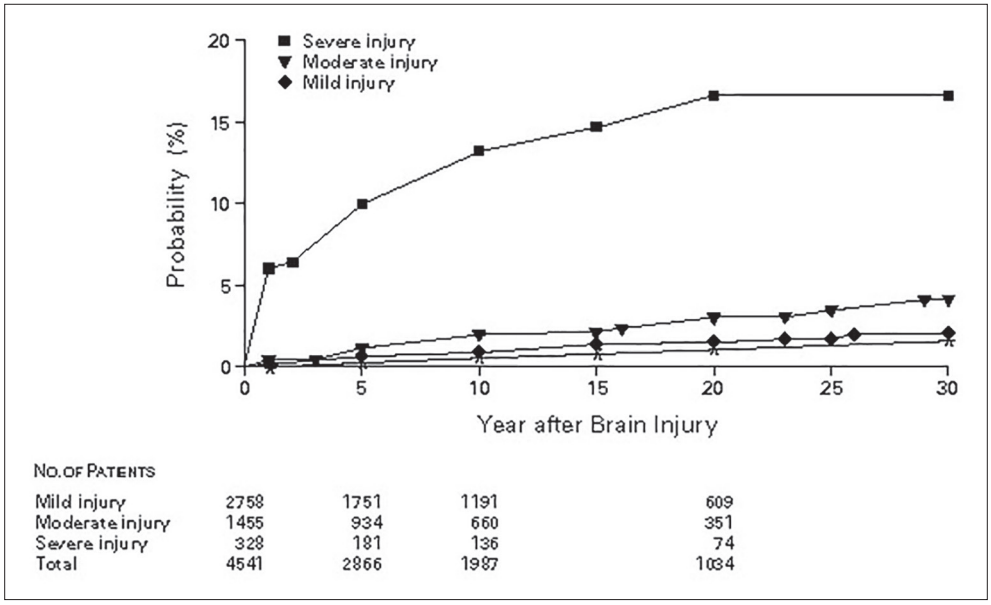

Figure 1. (Cumulative Probability of Unprovoked Seizures in 4541 Patients with Traumatic Brain Injuries, According to the Severity of the Injury and the Incidence of Seizures in the General Population, Annegers JF et al. N Engl J Med 1998; 338: 20–24.)

Table 1. (Annegers JF et al. N Engl J Med 1998; 338: 20–24.)

Table 1. Standardized Incidence Ratios for Seizures among 4541 Patients with Traumatic Brain Injury, According to the Severity of the Injury.

Severity of Injury*	No. of Cases		Standardized Incidence Ratio (95% CI)†
	Observed	Expected	
Mild	28	18.4	1.5 (1.0–2.2)
Moderate	30	10.5	2.9 (1.9–4.1)
Severe	39	2.3	17.0 (12.3–23.6)
Total	97	31.2	3.1 (2.5–3.8)

*Patients with mild injuries had a loss of consciousness or post-traumatic amnesia for less than 30 minutes, with no skull fracture; those with moderate injuries had a loss of consciousness or post-traumatic amnesia for 30 minutes to 24 hours or a skull fracture; and those with severe injuries had a brain contusion or intracranial hematoma or a loss of consciousness or post-traumatic amnesia for more than 24 hours.

†CI denotes confidence interval.

Table 2. (Annegers JF et al. N Engl J Med 1998; 338: 20–24.)

TABLE 2. STANDARDIZED INCIDENCE RATIOS FOR SEIZURES ACCORDING TO THE SEVERITY OF TRAUMATIC BRAIN INJURY AND THE INTERVAL AFTER THE INJURY.

INTERVAL AFTER INJURY (YR)	NO. OF PATIENTS*	NO. OF CASES		STANDARDIZED INCIDENCE RATIO (95% CI)†
		OBSERVED	EXPECTED	
Mild injury				
<1	2758	5	1.6	3.1 (1.0–7.2)
1–4	2483	11	5.2	2.1 (1.1–3.8)
5–9	1751	4	4.3	0.9 (0.3–2.6)
≥10	1191	8	7.4	1.1 (0.5–2.1)
Moderate injury				
<1	1455	6	0.9	6.7 (2.4–14.1)
1–4	1307	9	2.9	3.1 (1.4–6.0)
5–9	934	7	2.3	3.0 (1.2–6.2)
≥10	660	8	4.4	1.8 (0.8–3.6)
Severe injury				
<1	328	19	0.2	95.0 (58.4–151.2)
1–4	275	10	0.6	16.7 (8.4–32.0)
5–9	181	6	0.5	12.0 (4.5–26.6)
≥10	136	4	1.0	4.0 (1.1–10.2)

*The number of patients is the number being followed at the beginning of the interval.

†CI denotes confidence interval.

The Brain Trauma Foundation and the American Association of Neurological Surgeons published recommendations for anti-seizure prophylaxis in 2007. (Table 3.)

Young et al. published in 1983 a randomized, double blind study of 244 TBI patients to determine if the phenytoin was effective in prevention of early and late posttraumatic seizures. There was no significant difference in percentage of the number of patients with the early and late posttraumatic seizures in the treated and

Table 3. Recommendations for antiseizure prophylaxis. (Bullock R. et al. „Guidelines for the management of severe traumatic head injury", 2007.)

RECOMMENDATIONS	
Level 1	There are insufficient data to support a level 1 recommendations for this topic.
Level 2	Prophylactic use of phenytoin or valproate is not recommended for preventing late posttraumatic seizures. Anticonvulsants are indicated to decrease the incidence of early PTS (within 7 days after injury). However, early PTS is not associated with worse outcomes.

the placebo groups. The reason for phenytoin being ineffective in preventing early PTS may be explained by the low incidence of early PTS in the placebo and treatment groups. (13) This study leaves the possibility of phenytoin in high dosages being effective in PTS prevention.

Temkin et al. published in 1990 a randomized, double-blind study of 404 patients with severe traumatic brain injury, who received phenytoin or placebo. The phenytoin serum levels were maintained in the high therapeutic range. This study showed a 73% reduction of risk of early PTS in the phenytoin group. But there was no benefit in preventing the late PTS. (14)

Haltiner et al. performed in 1999 a secondary analysis on the same 404 patients to determine if the use of phenytoin in preventing the PTS was associated with significant adverse side effects and also to determine if the reduction in early posttraumatic seizures was associated with lower mortality rates. The incidence of drug-related side effects during the first two weeks of phenytoin treatment was low and not significantly different from the placebo group. Mortality rates in phenytoin and placebo groups were also similar. This study shows that phenytoin administration can effectively reduce early posttraumatic seizures without an increase in adverse drug effects. Reduction in the number of early PTS was not associated with a lower mortality rate. (15)

Temkin et al. published in 1999 a randomized, double-blind study to compare phenytoin to valproate effects in preventing the early PTS and valproate to placebo in preventing the late PTS. The rate of early seizures was similar in patients treated with phenytoin or valproate. Valproate therapy shows no benefits in reduction of the late PTS. In addition, there was a trend toward a higher mortality in the valproate group. That is the reason why valproate should not be routinely used for antiseizure prophylaxis. (16)

In 1992, Manaka demonstrated in his study that phenobarbital did not have any significant effects in the reduction of the late PTS. (17)

Studies which compared the effects of levetiracetam and phenytoin showed similar level of effectiveness in reduction of PTS following TBI. (18)

Based on the previous studies Greenberg suggested guidelines for initiation or discontinuation of antiepileptic drugs (AEDs). (Table 4.)

Table 4. Initiation and discontinuation of AEDs. (Greenberg et al.: „Handbook of Neurosurgery". 2010.)

INITIATION OF AEDs	DISCONTINUATION OF AEDs
Begin AEDs within 24 hours of injury in presence of any of high risk criteria When using phenytoin maintain high therapeutic levels Switch to phenobarbital if phenytoin not tolerated	Taper AEDs after one week of therapy except in the following: a. Penetrating brain injury b. Development of late PTS c. Prior seizure history d. Patient undergoing craniotomy
	For patient not meeting criteria to discontinue AEDs after 1 week: a. Maintain 6–12 months of therapeutic AED levels b. Recommend EEG to rule out seizure focus before discontinuation AEDs

CONCLUSION

We can conclude that the risk of PTS is correlated with the level of severity of traumatic brain injuries. Also, the severity of the injury was related to the period of the risk increase of the PTS).

The main risk factors for late seizures are brain contusion and subdural hematoma. The risk period for these patients is at least 20 years. Other risk factors include skull fractures and loss of consciousness for more than 24 hours.

Patients with mild head injuries (loss of consciousness or post-traumatic amnesia for less than 30 minutes) have moderate risk for PTS, but only for five years after the injury.

Administration of antiepileptics for seizure prophylaxis can reduce the early PTS but do not have effects on the late PTS. Routine seizure prophylaxis for the late PTS is not recommended. Antiepileptic administration for seizure prophylaxis is recommended only for early PTS, in the first 7 days following the injury. Phenytoin significantly reduces the incidence of the early PTS. Valproate has the similar effects to phenytoin, but may have a higher mortality and can't be routinely used for seizure prophylaxis. Levetiracetam demonstrates comparable effects to phenytoin for PTS prophylaxis.

Future trials should investigate effectiveness of antiepileptic drugs on patients with non-convulsive seizures.

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