Role of Anticonvulsants in the Management of Posttraumatic Epilepsy

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Posttraumatic seizures (PTS) have been recognized as a major complication of traumatic brain injury (TBI). The annual incidence of TBI in the United States is 1.7 million. The role of anticonvulsants in the treatment of posttraumatic epilepsy (PTE) remains uncertain. Based on current studies, however, anticonvulsants have been shown to reduce early PTS occurring within the first 7 days, but little to no benefits have been shown in late PTS occurring after 7 days. In this paper, we provide a mini review of the role of anticonvulsants and current advances in the management of PTE.

Keywords: posttraumatic seizures, traumatic brain injury, epilepsy, anticonvulsants, management

POSTTRAUMATIC EPILEPSY

Posttraumatic epilepsy (PTE) due to traumatic brain injury (TBI) has many causes, including wartime combat, vehicle accidents, work-related injuries, and sports injuries. Wartime combat injuries, especially blast injuries and penetrating head injuries (PTI), have shown to increase the risk of seizures, as that of blast models of TBI (1–4). The annual incidence of TBI is estimated to be 1.7 million in the United States, and seizures have been recognized as one of the major complications of this condition (5). The incidence of PTE was described by Annegers and colleagues who conducted a retrospective study in order to identify the characteristics of brain injuries that are associated with the development of seizures for 50 years. The results showed that the severity of the injury was correlated with the interval during which the risk of seizures was increased, even after more than 20 years post injury (6). The other study of interest was the Vietnam Head Injury Study (VHIS) that was a prospective, longitudinal follow-up of 1,221 Vietnam War Veterans who had PTI. The prevalence of PTE in this cohort was 45–53%. Patients with PTI carry a high risk of PTE even for decades; so, long-term medical follow-up is required (7). Similarly, the prospective study by Salazar and colleagues showed that seizure frequency in the first year predicted future severity of seizures. A higher seizure frequency was seen in the first year and was also associated with subjects having a longer duration of epilepsy and persistent seizures (8).

ROLE OF ANTICONVULSANTS IN THE MANAGEMENT OF POSTTRAUMATIC EPILEPSY

The seizures after head injury result in secondary brain damage, which involves increased intracranial pressure, increased metabolic brain demands post head injury, and excessive release of neurotransmitters,
which result in further complicating the existing damage. The main goal of anticonvulsants is to minimize the brain damage by preventing early seizures (9).

The other role of anticonvulsants apart from antiseizure activity is the neuroprotective effect, which has been demonstrated in animal models. Phenytoin, which is still considered as an agent of choice, has been shown to have neuroprotective properties in animal models. Vartanian and colleagues showed that phenytoin has been linked with decreased neuronal damage in neonatal rats following hypoxia (10). Another study by Tasker and colleagues showed similar results in rat hippocampal structures (11). Researchers suggested that neuroprotective effects were related to a blockage of voltage-dependent sodium channels during hypoxia, which decreased the spread of calcium-induced neurotoxicity following hypoxic brain injury (10, 11).

Posttraumatic seizures (PTS) are divided into two subgroups, early and late PTS. Early seizures occur within the first 7 days after brain injury, and late seizures occur after 7 days of injury. These definitions are important in terms of management and predicting prognosis of PTE (12).

The prospective randomized trials did not show promising results of the role anticonvulsants in the management of PTS. The randomized clinical trials are summarized in Table 1. No significant differences were seen in the treatment versus the non-treatment groups (13–20). Summary of selected non-randomized trials for posttraumatic seizure prevention was shown in Table 2, which also did not show a significant difference between groups (21–28).

Temkin and colleagues showed that phenytoin was considered effective in preventing provoked seizures and promising at preventing unprovoked seizures. Carbamazepine was considered effective in preventing provoked seizures after TBI, although its status was considered uncertain in preventing unprovoked seizures. Phenobarbital was considered promising at preventing provoked seizures and uncertain at preventing unprovoked seizures. Finally, the combination of phenytoin and phenobarbital was considered promising to prevent provoked and unprovoked seizures. It was also shown that provoked seizures showed promising results, but for unprovoked seizures, no drugs were shown to be effective. AEDs prescribed to prevent epileptogenesis should be avoided until clinical trials have found a drug for this purpose (29). Similarly, Chang and Lowenstein conducted a literature review of the evidence of AED prophylaxis in patients with severe TBI in order to guide better practice recommendations. Patients given phenytoin prophylaxis compared to controls had a significantly lower risk of early PTS in

### Table 1 | Summary of selected randomized controlled trials (RCT) for posttraumatic seizure prevention.

| Reference       | Study design | Number of patients randomized (N) | Methods                                                                 | Outcome                                                                 |
|-----------------|--------------|----------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Dikmen et al. (13) | RCT         | 124                              | Phenytoin versus placebo Patients were randomized to receive either PHT or placebo for 1 year and observed one more year without medication | No significant differences seen in neuropsychological examinations in 1 year between the 2 groups               |
| Temkin et al. (14) | RCT         | 123                              | Phenytoin versus placebo Treatment was started within 24 h of injury for 1 year and then 2 groups were followed for 2 years | Early seizures: improvement seen in the PHT GROUP Late seizures: no difference between the 2 groups |
| Young et al. (15)  | RCT         | 244                              | Phenytoin versus placebo Treatment was started within 24 h of injury | Early seizures: no difference between the 2 groups Late seizures: study was not designed to determine late seizure outcome |
| Young et al. (16)  | RCT         | 179                              | Phenytoin versus placebo Treatment was started within 24 h of injury and 2 groups were followed for 18 months to determine late seizure outcome | Early seizures: study was not designed to determine early seizure outcome Late seizures: no difference between the 2 groups |
| McQueen et al. (17) | RCT         | 164                              | Phenytoin versus placebo Two groups were followed for 2 years Occurrence of seizures was used as outcome measure | Early seizures: study was not designed to determine early seizure outcome Late seizures: no difference between the 2 groups |
| Szafiarski et al. (18) | RCT       | 52                               | Phenytoin versus levetiracetam Treatment was started within 24 h of injury between the 2 groups | Early seizures: no difference between the 2 groups Late seizures: study was not designed to determine late seizure outcome |
| Temkin et al. (19) | RCT         | 379                              | Phenytoin for 1 week versus valproate for 1 month versus valproate for 6 months Treatment was started within 24 h of injury Follow-up of these groups continued for 2 years | Early seizures: no difference among 3 groups Early seizures: no difference among 3 groups |
| Manaka (20)       | RCT         | 191                              | Phenytoin versus no treatment Treatment was started within 4 weeks post head injury They received full dose for 2 years and tapered off in third year Follow-up in 5 years | Early seizures: study was not designed to determine early seizure outcome Late seizures: no difference among 3 groups |
The role of anticonvulsants in early PTS seems favorable as compared to late PTS. Anticonvulsants are found to be effective in patients who develop PTE.

Phenytoin remains the most commonly used anticonvulsant, but the side effects do favor the use of newer anticonvulsants, e.g., levetiracetam because of lack of drug–drug interactions and availability in parenteral form. The cognitive side effects and non-linear kinetics limit the use in certain patient populations. Carbamazepine has shown to be effective but drug–drug interactions and unavailability in parenteral form limits the use.

### TABLE 2 | Summary of selected non-randomized trials for posttraumatic seizure prevention.

| Reference | Study design | Number of patients randomized (N) | Methods | Outcome |
|-----------|-------------|---------------------------------|---------|---------|
| Servit and Musil (21) | Non-RCT | 167 | Treatment group (n = 143) were administered phenytoin or phenobarbital. Control group (n = 24) where conventional treatment was used. Duration: 2 years | Early seizures: not applicable. Late seizures: 25% in the control group and 2.1% in the treatment group. |
| Inaba et al. (22) | Prospective controlled trial | 813 | Participants were administered either levetiracetam or phenytoin for 7 days | Early seizures: no difference between the 2 groups. Late seizures: not applicable. |
| Kruer et al. (23) | Retrospective cohort | 109 | Retrospective review of patients who received levetiracetam or phenytoin | Early seizures: no difference between the 2 groups. Late seizures: not applicable. |
| Gabriel and Rowe (24) | Cohort | 19 | Participants were divided based on levetiracetam and phenytoin prophylaxis. Follow-up interview conducted to assess seizure outcome | Early seizures: no difference between the 2 groups. Late seizures: no difference between the 2 groups. |
| Jones et al. (25) | Cohort | 27 | Phenytoin versus levetiracetam administered during first 24 h post severe TBI | Early seizures: no difference between the 2 groups. Late seizures: not applicable. |
| Bhullar et al. (26) | Case-control | 93 | Phenytoin versus no treatment to determine occurrence of early seizures | Early seizures: no difference between the 2 groups. Late seizures: not applicable. |
| Formisano et al. (27) | Retrospective and prospective | 137 | Anticonvulsants versus no treatment. Study 1: prospective. Study 2: retrospective | Study 1: No difference between the 2 groups. Study 2: Late seizures higher in the treated group. |
| Watson et al. (28) | Cohort | 404 | Glucocorticoids administered within 1 day versus no glucocorticoids | Early seizures: not applicable. Late seizures: no difference between the 2 groups. |
of this agent. Neurocognitive side effects were also seen in other older anticonvulsants, including Phenobarbital, which may mask the mental status findings in TBI patients because of the sedating effects. Valproate can cause coagulopathy which may result in intracranial hemorrhage (30, 31).

Unfortunately, limited scientific data exist, which are specific to PTE with other anticonvulsants, and there is a need for additional controlled randomized clinical trials to explore more options.

**NEW DIRECTIONS IN THE MANAGEMENT OF POSTTRAUMATIC EPILEPSY**

The PTE can be differentiated from PTS that are sequelae from TBI. The term PTE signifies recurrent seizure disorder due to TBI. The PTE can be differentiated from PTS that are sequelae from intracranial hemorrhage (30, 31).

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Kirmani et al.

Anticonvulsants in Posttraumatic Epilepsy

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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