ORIGINAL RESEARCH PAPER

Anesthesiology

COMPARISON OF LEVETIRACETAM WITH PHENYTOIN IN THE SECOND LINE TREATMENT OF CONVULSIVE STATUS EPILEPTICUS

KEY WORDS: Convulsions, status epilepticus, phenytoin, levetiracetam.

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ABSTRACT

Background: One of the most common and serious conditions which is associated with high mortality (20%) in Intensive care units is status epilepticus. Urgent treatment is necessary to control seizures as significant irreversible brain injury occurs without treatment. Though benzodiazepines such as lorazepam or diazepam or Midazolam are used as first line agents to gain seizure cessation, often second line antiepileptics such as phenytoin or levetiracetam or valproate are used to prevent seizure recurrences. However, studies regarding the efficacy of these three antiepileptic drugs in the management of status epilepticus are few. Hence, this study is conducted to know whether phenytoin or levetiracetam can be used as a first choice drug. **Materials and Methods:** Present study is conducted on 88 patients who were presented to emergency departments in different hospitals in Andhra Pradesh with generalized status epilepticus during the period between Jan 2020 and December 2020. 40 patients were treated with phenytoin and 48 patients were given levetiracetam. **Results:** Among 40 patients who were treated with phenytoin, 28 patients achieved seizure cessation. Among 48 patients who were treated with levetiracetam, 36 patients achieved seizure cessation within 60 minutes. **Conclusion:** Phenytoin and Levetiracetam are equally efficacious in termination of seizures within 60 minutes in patients with generalized status epilepticus.

INTRODUCTION:

Status epilepticus (SE), a life threatening illness, is common among ICU patients in both developed and developing countries. Convulsive SE is common in patients who are affected more with various nervous system and multisystemic infections like tuberculosis and other microbial infections. Others include conditions with raised intracranial tension like intracranial hemorrhage, massive infarction of brain, neoplasms, meningitis or encephalitis, cerebral venous sinus thrombosis, and traumatic brain injury, and metabolic derangements, drug withdrawal, anoxia, and drug overdose.[1]

In adults, Status Epilepticus is characterized by a persistent seizure episode for more than 5 minutes, or two discrete seizure episodes with no complete recovery of consciousness in between. Longer the episode lasts, shorter the chances of spontaneous cessation of seizures, more difficult it becomes to manage seizure cessation, and more brain damaging effects would occur and hence prompt treatment is necessary immediately.[2]

Generalized status epilepticus is unusually detrimental and hence early cessation of seizures is the primary goal.[2] The first line treatment to achieve seizure cessation comprises the administration of different benzodiazepines such as lorazepam, diazepam or midazolam. However, in 40 percent of patients, seizure cessation is not achieved and progresses to established convulsive status epilepticus in spite of adequate treatment with first line drugs such as benzodiazepines. Hence, the second line treatment with a loading dose of antiepileptic drugs is often necessary in such patients.[2,3] Following antiepileptic drugs such as valproate, phenytoin or fosphenytoin, levetiracetam, lacosamide or phenobarbital can be used for convulsive status epilepticus. However, evidence regarding the relative superiority of different drugs as first choice among them is scarce.[2,3] Hence, the present study is done to compare the efficacy of various anti epileptic drugs like Phenytoin and Levetiracetam in the management of seizures in convulsive SE.

MATERIALS AND METHODS:

Present study is conducted after collecting data from emergency departments in different hospitals across different regions of Andhra Pradesh. Around 302 patients, in the age group between 18 and 65 years, who presented with seizures to the emergency department were selected initially between January 2019 to September 2019. Of them, 188 patients had no convulsive status epilepticus. Hence, their details were removed. And 26 patients did not throw fits after treatment with first line drugs such as intravenous lorazepam or midazolam. Remaining 88 patients had thrown fits even after administration of first line drugs, and hence, they were included in the study.

Of them, intravenous phenytoin was randomly allocated to 40 patients and 48 patients were assigned intravenous levetiracetam. Intravenous phenytoin was given as 15-20 mg/kg within 20 minutes (maximum dose of 50 mg/min) and intravenous levetiracetam was given as 60 mg/min within 5 minutes (upto a maximum dose of 4,500 mg at a maximum rate of 6 mg/kg/min). And the primary outcome of seizure cessation within 60 minutes after the administration of individual drugs is counted. The study was done after obtaining consent after explaining the benefits and risks of drugs to patient attenders in some cases. However, consent could not be obtained in some cases because of the emergency condition and need for faster and rapid interventions to save a patient.

Statistical Analysis

The data was entered into MS excel and analyzed using SPSS 2.0 software.

Eligibility Criteria:

Inclusion criteria (population, interventions, comparisons, outcomes and study design):

Population:

Patients with a single and persistent seizure episode lasting for more than 5 minutes without spontaneous cessation, and patients who had more than 2 discrete seizure episodes without complete regaining of consciousness in between two episodes in spite of treatment with first line antiepileptic drugs such as benzodiazepines.

Intervention: Intravenous levetiracetam.

Comparison: Intravenous phenytoin.

Outcome: The primary outcome was cessation of seizures within 60 minutes.

Study design: Randomized clinical trial.

Exclusion Criteria:
Patients who had seizures with spontaneous cessation within 5 minutes and other types of seizures such as myoclonic or absence or non-convulsive types.

RESULTS:
Of 88 patients, 40 patients (45.45%) were treated with intravenous phenytoin and 48 patients were treated with intravenous levetiracetam. Of the 40 patients who were treated with phenytoin, 28 patients were males and 12 patients were females. Of the 48 patients (55.55%) who were treated with intravenous levetiracetam, 38 patients were males and 10 patients were females. 20 male patients and 8 female patients gained seizure cessation (70% of patients) within 60 minutes after treatment with intravenous phenytoin. That is, 28 male patients and 8 female patients (75% of patients) out of 48 patients had complete seizure stoppage within an hour after the administration of loading dose of introducing levetiracetam.

Table 1 showing the results of the study

Characteristics	Phenytoin (n=40) (45.45%)		Levetiracetam (n=48) (54.55%)	
Outcome	Controlled	Uncontrolled	Controlled	Uncontrolled
No. of patients	28 (70%)	12 (30%)	36 (75%)	12 (25%)
Males	20	08	28	10
Females	08	04	08	02

DISCUSSION:
According to the International League Against Epilepsy (ILAE) Task Force on classification of Status Epilepticus is defined as "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures…that can have long-term consequences…including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures."[4] Diagnosis is made by physical signs such as tonic-clonic seizures, and confirmed by electroencephalogram.[2]

Diagnosing a case of Status Epilepticus is important as a diagnostic challenge arises when patients have no physical signs such as tonic-clonic seizures as in nonconvulsive status epilepticus, but response is good with antiepileptic drugs. Main strategy is to secure the airway, IV cannula for drug administration, stopping the seizure activity, and finding and correcting the underlying cause. Intravenous administration of Benzodiazepines is regarded as first line management of Status Epilepticus.[2,3] But intravenous drugs like Fosphenytoin, Phenytoin, Levetiracetam, Valproic acid and Midazolam can also be used. The relative efficacy of different drugs as first choice is scarcely studied.[3] Hence, this study is performed to compare the efficacy of intravenous levetiracetam with intravenous phenytoin to determine whether any drug can be used as a first choice in the management of established status epilepticus.

In our study, around 70 percent of patients who were treated with intravenous phenytoin achieved seizure remission within 60 minutes. Whereas the percentage of patients who received intravenous levetiracetam and attained seizure cessation was 75 percent. And the difference between phenytoin and levetiracetam is significantly less in terms of time required to achieve seizure cessation. Our study is in the line with many other studies which demonstrate more or less similar results in children and adults as well.

A study conducted by Kapur et al.[5] on 384 patients revealed similar efficacy of three antiepileptic drugs such as fosphenytoin, levetiracetam and valproate in seizure cessation and improved alertness within 60 minutes in half of the patients assigned with respective drugs.

Another study conducted by Kumar S et al.[6] on 50 children with status epilepticus revealed faster cessation of seizures in a group of patients that were treated with fosphenytoin when compared with that of patients treated with levetiracetam. However, other parameters such as seizure control rate, seizure free duration, PICU stay, hospital stay and seizure recurrence were similar with both drugs.

A study conducted in 13 emergency departments in Australia and Newzealand among 233 children with status epilepticus also revealed levetiracetam as not superior to phenytoin. In this study by Dalziel et al.[7] 114 patients were assigned with phenytoin and 119 patients were assigned with levetiracetam. Around half of patients in both groups achieved remission with any of the drugs and hence, both phenytoin and levetiracetam were similar in efficacy.

Another study conducted by Lyttle et al.[8] in 30 emergency departments in the United Kingdom on 286 patients also revealed levetiracetam as not significantly superior to phenytoin, and around 70 percent of patients had seizure cessation within one hour with the use of any of both drugs.

Another study conducted by Chakravarthy et al.[9] also demonstrated more or less similar findings. Phenytoin was efficacious in 68.2% of patients assigned, whereas levetiracetam was effective among 59.1% of patients of the total allocated. And hence, that study also declared levetiracetam and phenytoin as equally efficacious.

Another study by Mundlamani et al.[10] also revealed three antiepileptic drugs such as phenytoin, valproate, and levetiracetam as equally efficacious after conducting a study among 150 patients that were presented with status epilepticus to the emergency department.

CONCLUSION:
Though benzodiazepines are used as the first line drugs in the management of convulsive status epilepticus, they are not always completely successful. Hence, the use of second line antiepileptic drugs such as valproate, levetiracetam, and phenytoin is necessary in around 40 percent of patients. However, the evidence regarding the usage as first choice among those second line drugs is scarce. This study compared the efficacy of levetiracetam and phenytoin in controlling seizures in convulsive status epilepticus. It is found that levetiracetam may not be significantly advantageous over phenytoin in terms of seizure cessation in patients with convulsive SE.

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