



Levetireacetam Versus Phenytoin in management of Pediatric Status Epilepticus

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Abstract: Introduction: Status epilepticus can cause significant morbidity and mortality. These can be reduced by early effective treatment. The cause of SE is the most important determinant of outcome. Febrile SE is associated with less morbidity compared to other causes of SE. The earlier the treatment is started, the more likely the control of SE and less likely to develop subsequent neurological deficits or epilepsy. Resistance to first and second line treatments for SE is directly related to the duration of seizures prior to treatment. **Aim of Work:** was to compare the efficacy and side effects of Levetireacetam and Phenytoin in management of pediatric status epilepticus. **Subject and Methods:** this study was conducted on 60 children suffering from status epilepticus who were admitted to Pediatric Neurology Unit and Pediatric intensive care unit (PICU) of Tanta University Hospital. **Results:** status epilepticus was controlled in 14 patients (46.67%) in Levetireacetam group and in 21 patients (70%) in Phenytoin group. The difference was statistically insignificant. Side effect reported in Levetireacetam group were dizziness in 6 patients (20%) and abnormal behavior in 4 patients (13.33%). In Phenytoin group side effects were bradycardia in 1 patients (3.33%) and extravasation in 2 patients (6.67%). **Conclusion:** Phenytoin was insignificantly more effective than Levetireacetam in controlling status epilepticus in children. No serious side effects were reported in Levetireacetam or Phenytoin group.

[Amany E. Mouslam, Amira H. Darwish, Ahmed A. Abo Elezz, Azza K. El-Shahawy. **Levetireacetam Versus Phenytoin in management of Pediatric Status Epilepticus.** *J Am Sci* 2020;16(10):46-52]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). <http://www.jofamericanscience.org>. 5. doi:[10.7537/marsjas161020.05](https://doi.org/10.7537/marsjas161020.05).

Key Words: status epilepticus-antiepileptic drugs, Phenytoin. Levetireacetam.

1. Introduction:

Status epilepticus is now defined as a single seizure lasting more than five minute or two or more seizure within a five-minute without the person return to normal between them (**Chin et al., 2004**).

These children are also at increased risk of irreversible morbidity including chronic drug-resistant epilepsy, neurodisability and learning difficulties, which result in major long-term demands on acute and chronic health and social care resources.

The current UK emergency care pathway for the management of childhood convulsive status epilepticus (CSE) is the step-wise algorithm advocated in advanced pediatric life support (**Wiley, 2016**).

Aim of the Work:

The aim of this work was to compare the efficacy of Levetireacetam and Phenytoin in management of pediatric status epilepticus.

2. Patients and Methods:

Subjects:

This study was conducted on 60 children suffering from status epilepticus who were admitted to Pediatric Neurology Unit and Pediatric intensive care unit (PICU) of Tanta Hospital University.

Duration of the Study:

The study period extended from August 2018 to September 2019.

Study design: randomized clinical trial.

Inclusion Criteria:

Children suffering from convulsive generalized tonic clonic status epileptics at any age.

Exclusion Criteria:

Children suffering from the following were excluded from the study:

1. Non convulsive status epilepticus.
2. Children with known contraindication or allergy to levetireacetam or phenytoin.
3. Children suffering from any illness other than epilepsy e.g. renal, hepatic, cardiac....etc.

Outcome measures:

-The primary outcome was cessation of all visible signs of convulsive status epilepticus activity.

-The secondary outcomes were:

- 1) Need for further anticonvulsant to manage seizure after randomized treatment.
- 2) Need for admission to a PICU.
- 3) Serious complications, cardiovascular instability, extravasation injury, and extreme agitation.

Randomization and recruitment:

- Eligible children were randomized following completion of first-line therapy if the convulsive status

- epilepticus was continuing, enabling preparation and administration of the allocated treatment.

- Patients were divided into two groups: Group I: received Levetireacetam, Group II: received Phenytoin.

- Patients were randomized to levetireacetam or phenytoin in a ratio of 1:1.

Trial Treatments:

- A single dose of the randomly allocated treatment was administered by IV infusion.

- The Levetireacetam dose is 20-40 mg/kg over 5 minute, diluted to a 50 mg/ml with 0.9% sodium chloride.

- Phenytoin dose is 20 mg/kg/min, diluted with 0.9% sodium chloride to a maximum concentration of 10 mg/ml, at rate 1mg/kg/min.

Methods:

All patients were subjected to the following:

- 1) Complete history taking.
- 2) Thorough clinical examination including neurological examination.
- 3) EEG.
- 4) Laboratory investigations:
 - Arterial blood gas
 - Serum electrolyte:) Na, K, Ca, Mg (.
 - Anti epileptic drug level in patients using antiepileptic drug
- 5) MRI brain

Statistical Methods:

Data were revised, coded and entered to the statistical package for social science (SPSS) version 22 (Pallant, 2007).

3. Results:

Table (1): Age of the studied groups

| Age (Years) | Levetireacetam group (n=30) | | Phenytoin group (n=30) | | P-value |
|---------------|-----------------------------|-------------|------------------------|-------------|---------|
| Range | 1 | - 10 | 1 | - 11 | 0.636 |
| Mean \pm SD | 5.833 | \pm 3.494 | 6.279 | \pm 3.748 | |

In Levetireacetam group the range of age was 1-10 years and the mean was 5.833 ± 3.494 years. In Phenytoin group the range of age was 1-11 years and

the mean age was 6.279 ± 3.748 years. The difference was statistically insignificant.

Table (2): Sex of the studied groups

| Sex | Levetireacetam group (n=30) | | Phenytoin group (n=30) | | Total (n=60) | | Chi-Square | |
|--------|-----------------------------|--------|------------------------|--------|--------------|--------|----------------|---------|
| | n | % | n | % | n | % | X ² | P-value |
| Male | 20 | 66.67 | 18 | 60.00 | 38 | 63.33 | 0.287 | 0.592 |
| Female | 10 | 33.33 | 12 | 40.00 | 22 | 36.67 | | |
| Total | 30 | 100.00 | 30 | 100.00 | 60 | 100.00 | | |

In Levetireacetam group 20 patients were males (66.67%) and 10 patients were females (33.33%). In Phenytoin group 18 patients were males (60%) and 12

patients were females (40%). The difference was statistically insignificant.

Table (3): Etiology of status epilepticus in the studied groups

| Etiology | Levetireacetam | | Phenytoin | | Total | | Chi-Square | |
|---------------------------------|----------------|--------|-----------|--------|-------|--------|----------------|---------|
| | N | % | N | % | N | % | X ² | P-value |
| Uncontrolled epilepsy | 11 | 36.67 | 9 | 30.00 | 20 | 33.33 | 1.700 | 0.889 |
| Intracranial haemorrhage | 5 | 16.67 | 7 | 23.33 | 12 | 20.00 | | |
| Brain thrombosis | 5 | 16.67 | 3 | 10.00 | 8 | 13.33 | | |
| Hypoxic ischemic encephalopathy | 4 | 13.33 | 4 | 13.33 | 8 | 13.33 | | |
| Prolonged febrile seizure | 3 | 10.00 | 3 | 10.00 | 6 | 10.00 | | |
| Idiopathic | 2 | 6.67 | 4 | 13.33 | 6 | 10.00 | | |
| Total | 30 | 100.00 | 30 | 100.00 | 60 | 100.00 | | |

In Levetireacetam group the etiology of status epilepticus was uncontrolled epilepsy in 36.67% of patients, intracranial haemorrhage in 16.67% of

patients, brain thrombosis in 16.67% of patients, hypoxic ischaemic encephalopathy in 13.33% of patients, Prolonged febrile seizure in 10% of patients

and idiopathic in 6.67% of patients. In Phenytoin group the etiology of status epilepticus was uncontrolled epilepsy in 30% of patients, intracranial haemorrhage in 23% of patients, brain thrombosis in

10% of patients, hypoxic ischaemic encephalopathy in 13.33% of patients, Prolonged febrile seizure in 10% of patients and idiopathic in 13.33% of patients.

Table (4): Family history of epilepsy in the studied groups

| Family history of epilepsy | Levetireacetam | | Phenytoin | | Total | | Chi-Square | |
|----------------------------|----------------|--------|-----------|--------|-------|--------|----------------|---------|
| | n | % | n | % | n | % | X ² | P-value |
| Negative | 26 | 86.67 | 24 | 80.00 | 50 | 83.33 | 0.480 | 0.488 |
| Positive | 4 | 13.33 | 6 | 20.00 | 10 | 16.67 | | |
| Total | 30 | 100.00 | 30 | 100.00 | 60 | 100.00 | | |

In Levetireacetam group family history of epilepsy was positive in 13.33% and negative in 86.67% of patients. In Phenytoin group family history of epilepsy was positive in 20% and negative in 80% of patients.

Table (5): MRI Brain findings in the studied groups

| MRI Brain | Levetireacetam | | Phenytoin | | Total | | Chi-Square | |
|-------------------------|----------------|--------|-----------|--------|-------|--------|----------------|---------|
| | n | % | n | % | n | % | X ² | P-value |
| Normal | 15 | 50.00 | 17 | 56.67 | 32 | 53.33 | 0.960 | 0.811 |
| Intracranial hemorrhage | 8 | 26.67 | 5 | 16.67 | 13 | 21.67 | | |
| Brain atrophy | 4 | 13.33 | 4 | 13.33 | 8 | 13.33 | | |
| Cerebral infraction | 3 | 10.00 | 4 | 13.33 | 7 | 11.67 | | |
| Total | 30 | 100.00 | 30 | 100.00 | 60 | 100.00 | | |

In Levetireacetam group MRI brain was normal in (50%) of patients, intracranial hemorrhage in (26.67%), brain atrophy in (13.33%) of patients and cerebral infraction in (10%) of patients. In Phenytoin

group MRI brain was normal in (56.67%) of patients, intracranial hemorrhage in (16.67%), brain atrophy in (13.33%) of patients and cerebral infraction in (13.33%) of patients.

Table (6): EEG findings in the studied group

| EEG | Levetireacetam | | Phenytoin | | Total | | Chi-Square | |
|------------------------|----------------|--------|-----------|--------|-------|--------|----------------|---------|
| | N | % | N | % | N | % | X ² | P-value |
| Normal | 10 | 33.33 | 8 | 26.67 | 18 | 30.00 | 0.317 | 0.573 |
| Epileptogenic activity | 20 | 66.67 | 22 | 73.33 | 42 | 70.00 | | |
| Total | 30 | 100.00 | 30 | 100.00 | 60 | 100.00 | | |

In Levetireacetam group EEG findings was normal in 33.33% of patients and showed epileptogenic activity in 66.67% of patients. In

Phenytoin group EEG findings was normal in 26.67% of patients and showed epileptogenic activity in 73.33% of patients.

Table (7): Outcome of status epilepticus in the studied group

| Outcome | Levetireacetam group (n=30) | | Phenytoin group (n=30) | | Total (n=60) | | Chi-Square | |
|--------------|-----------------------------|--------|------------------------|--------|--------------|--------|----------------|---------|
| | N | % | N | % | N | % | X ² | P-value |
| Controlled | 14 | 46.67 | 21 | 70 | 35 | 58.33 | 2.469 | 0.116* |
| Uncontrolled | 16 | 53.33 | 9 | 30 | 25 | 41.67 | | |
| Total | 30 | 100.00 | 30 | 100.00 | 60 | 100.00 | | |

*Significant p value<0.05

In Levetireacetam groups 14 patients (46.67%) were controlled and 16 patients (53.33%) were uncontrolled, in Phenytoin group 26 patients (86.67%)

were controlled and 4 patients (33.33%) were uncontrolled. The difference was statistically significant.

Table (8): Side effects of drug in the studied groups

| Side Effect | Levetireacetam group (n=30) | | Phenytoin group (n=30) | | Total (n=60) | | Chi-Square | |
|-------------------|--------------------------------|--------|---------------------------|--------|-----------------|--------|----------------|---------|
| | N | % | N | % | N | % | X ² | P-value |
| No | 20 | 66.67 | 27 | 90.00 | 47 | 78.33 | 14.043 | 0.007* |
| Abnormal behavior | 4 | 13.33 | 0 | 0.00 | 4 | 6.67 | | |
| Dizziness | 6 | 20.00 | 0 | 0.00 | 6 | 10.00 | | |
| Bradycardia | 0 | 0.00 | 1 | 3.33 | 1 | 1.67 | | |
| Extravasation | 0 | 0.00 | 2 | 6.67 | 2 | 3.33 | | |
| Total | 30 | 100.00 | 30 | 100.00 | 60 | 100.00 | | |

*Significant p value<0.05

Side effect reported in Levetireacetam group were dizziness in 6 patients (20%) and abnormal behavior in 4 patients (13.33%). In Phenytoin group side effects were bradycardia in 1 patient (3.33%) and extravasation in 2 patients (6.67%).

4: Discussion:

Status epilepticus can cause significant morbidity and mortality. These can be reduced by early effective treatment (**Lambrechse and Buchhalter, 2008**).

The cause of SE is the most important determinant of outcome. Febrile SE is associated with less morbidity compared to other causes of SE. The earlier the treatment is started, the more likely the control of SE and less likely to develop subsequent neurological deficits or epilepsy. Resistance to first- and second-line treatments for SE is directly related to the duration of seizures prior to treatment (**Hussain et al., 2007**).

The present clinical trial evaluated the efficacy of intravenous Levetireacetam compared to intravenous Phenytoin in treatment of SE in children. Phenytoin was insignificantly more effective than Levetireacetam. In Levetireacetam groups 14 patients (46.67%) were controlled and 16 patients (53.33%) were uncontrolled. In Phenytoin group 21 patients (70%) were controlled and 9 patients (30%) were uncontrolled.

This agrees with **Dalziel et al., 2019** who found that control of SE occurred within 5 min of drug infusion in 60% of patients in Phenytoin group and 50% of patients in the levetireacetam group.

The study done by **Lytte et al., 2019** reported that Levetireacetam is as effective as phenytoin for controlling prolonged epileptic seizures in children. In this trial, SE was controlled by levetireacetam in 70% of children and in 64% of children in phenytoin group.

Also **Chakravarthi et al., 2015** reported that Phenytoin achieved control of SE in 68.2% patients compared to Levetireacetam in 59.1%.

Appleton et al., 2019 reported that SE was terminated in 69.6% of the levetiracetam, and 64.2% of the phenytoin-treated group.

The study done by **Singh et al., 2018** on 100 children aged 3–12 years of age presenting with acute SE found that efficacy of Phenytoin was obtained in 96% and efficacy of Levetireacetam was obtained in 94%.

However **Wani et al., 2019** found that seizure control was better in Levetiracetam group (96%) compared with Phenytoin group (59.6%).

Also, Levetiracetam and Phenytoin were found to be effective in control of CSE in 92.7% and 83.3% of patients respectively (**Noureen et al., 2019**).

In the present study, the mean age in Levetireacetam group was 1-10 year and 1-11 year in Phenytoin group. This comes in agreement with the findings of **Hussein et al., 2007** (who reported that the mean age of children suffered from status epilepticus was 3 month-15 year).

Singh et al., 2018 reported that status epilepticus occurred in children between 3-12 years.

Nishiyama et al., 2007 study reported that, the highest incidence of SE (155.1/100,000) was seen in the age range of 31 days or older to <1 year, followed by 101.5/100,000 in the age range of one year, and the incidence decreased after eight years.

As regard sex distribution among studied group, In Levetireacetam group 20 patients were males (66.67%) and 10 patients were females (33.33%). In Phenytoin group 18 patients were males (60%) and 12 patients were females (40%), this is in agreement with the study conducted by **Noureen et al., 2019** who reported that in Levetireacetam group (72%) were males and (28%) were females. In Phenytoin group (63.3%) were males and (36.7) were females.

In the study done by **Lytte et al., 2019** 49% patients were males and 51% were females in Levetireacetam group. In Phenytoin group 54% were males and 46% were females.

In the present study etiology of status epilepticus in Levetireacetam group was uncontrolled epilepsy in 53.33% of patients, brain thrombosis in 6.67% of patients, intracranial haemorrhage in 20% of patients, cerebral infraction in 6.67% of patients and hypoxic ischaemic encephalopathy in 13.33% of patients. In Phenytoin group the etiology of status epilepticus was uncontrolled epilepsy in 20% of patients, intracranial haemorrhage in 13.33% of patients, cerebral infraction in 6.67% of patients and hypoxic ischaemic encephalopathy in 13.33% of patients.

While the study done by **(Lyttle et al., 2019)** reported that etiology of status epilepticus in Levetireacetam group was prolonged febrile convulsion in 41%, uncontrolled epilepsy in 30%, first afebrile seizure in 11%, CNS infection in 4%, intracranial vascular event in 1%, substance misuse in < 1%, indeterminate in 7% and other in 18%. In Phenytoin group the etiology of SE was prolonged febrile convulsion in 43%, uncontrolled epilepsy in 34%, first afebrile seizure in 9%, CNS infection in 5%, intracranial vascular event in 1%, indeterminate in 5% and other in 19%.

Noureen et al., 2019 reported that cause of SE in Levetireacetam group was CNS infection in 43.3%, prolonged febrile seizure in 6%, uncontrolled epilepsy in 17.3, cerebral palsy in 19.3% and neurodegenerative disorders in 14%. In Phenytoin group etiology was CNS infection in 40%, prolonged febrile seizure in 6.7%, uncontrolled epilepsy in 16.6, cerebral palsy in 20.7% and neurodegenerative disorders in 16%.

Also **Chin et al., (2006)** study done on 266 children with status epilepticus, reported that 56% children were neurologically healthy before their first episode and 57% of those children had a prolonged febrile seizure. 12% of children with first febrile convulsive status epilepticus had acute bacterial meningitis.

Hussain et al., (2007) study on 137 children with SE showed that 34% were admitted following a prolonged febrile seizure, 28% had a remote symptomatic cause for the CSE, 18% were admitted for an acute symptomatic cause and 11% were admitted with an acute exacerbation of a pre-existing idiopathic epilepsy. Six children had a progressive encephalopathy and no cause was identified in the remaining 7 of the 137 children 5%. Forty-nine 36% of the 137 children had pre-existing epilepsy.

Epidemiological study of SE on 37 Japanese children (31 days or older to <15 years of age) in Okayama City reported that, Febrile SE in the absence of CNS infection accounted for 17 patients. Acute symptomatic etiologies other than febrile SE were observed in eight patients, including three cases of influenza encephalitis. Five were classified as remote

symptomatic and the remaining seven as cryptogenic **(Nishiyama et al., 2007)**.

Shinnar et al., (1997) reported that, the distribution of causes was highly age dependent. More than 80% of children younger than 2 years had SE of febrile or acute symptomatic origin, whereas cryptogenic and remote symptomatic causes were most common in older children. 40% of the cases were known to be previously neurologically abnormal, including 21% of 169 younger than age 2 years and 55% of 225 older than 2 years.

The study done by **Chegondi et al., (2019)** reported that 36.7% of all children with SE had no etiology found, 10.8% had febrile seizures, and the remaining children had meningitis, encephalitis, or space-occupying lesions.

In this study, 30-minutes EEG was normal in 33.33% of patients in Levetireacetam group and 26.67% of patients in Phenytoin group. Epileptogenic activity showed in 66.67% of patients in Levetireacetam group and 73.33% of patients in Phenytoin group.

Chegondi et al., (2019) reported that about 75% of their patients with convulsive status epilepticus had EEG monitoring, and 70% of them had abnormal EEGs.

Sahin et al., (2016) reported that EEGs were performed in 29 patients, 20% had normal findings, whereas 17.8% had diffuse background slowing. Electrographic seizures were found in 17.8% patients with focal epileptiform discharges and 8.9% patients with generalized epileptiform discharges.

As regard MRI brain in this study: in Levetireacetam group MRI brain was normal in 50% of patients, intracranial hemorrhage in 26.67%, brain atrophy in 13.33% of patients and cerebral infraction in 10% of patients. In Phenytoin group MRI brain was normal in 56.67% of patients, intracranial hemorrhage in 16.67%, brain atrophy in 13.33% of patients and cerebral infraction in 13.33% of patients.

Abnormal findings on imaging were noted in 45.7% of patients in the study done by **(Chegondi et al., 2019)**.

The study done by **Nair et al., (2009)** on 99 patients with status epilepticus reported that MRI brain showed cortical lesion in 10% of patients, subcortical lesion in 19% of patients and both cortical and subcortical lesion in 30%.

In this study side effects reported in Levetireacetam group were dizziness in 6 patients (20%) and abnormal behavior in 4 patients (13.33). In Phenytoin group side effects were bradycardia in 1 patients (3.33%) and extravasation in 2 patients (6.67%).

Noureen et al., (2019) reported that adverse drug reactions were noted in 2.7% children treated with

Phenytoin. Cardiac and respiratory depression were noted in 0.7% and 2.0% children who were treated with Phenytoin.

Singh et al., (2018) reported that behavioral side effects in form of aggressive behavior or oppositional behavior were seen in 12.7% of patients, followed up till 7 days in the levetireacetam group.

Farooq et al., (2019) reported that the most serious adverse effects associated with levetireacetam use are behavioral disturbances and were more common in patients with a history of psychiatric and neurobehavioral problems.

In the study done by **Perry and Benatar, (2007)** they found that side effects of Levetireacetam occurred in 34% of subjects but required discontinuation in only 16%, most commonly because of behavioral disturbances.

On the other hand the study done by **Kirmani et al., (2009)** on thirty-two patients found that no serious side effects were evident during intravenous administration of Levetireacetam.

Appleton and Gill, (2003) reported that 27% patients treated with intravenous Phenytoin experienced one or more side-effects, including extravasation of the drug, hypotension and cardiac arrhythmia.

Also **Lyttle et al., (2019)** reported extravasation in 3% of patients with convulsive status epilepticus treated with intravenous phenytoin.

Limitations:

The small number of patients who included in this trial was a limitation of the study. Therefore, it is very important to perform another extensive study on a large number of children to confirm which is better for Pediatric SE, Levetireacetam or Phenytoin. Another limitation of this study was that we had no chance to do continuous EEG monitoring. Therefore, evaluation of seizure control was based on clinical assessment of patients and 30-minutes EEG recording.

Advantages of the study:

The present clinical trial has low risk of selection bias as randomization and allocation concealment were done.

Conclusion:

Phenytoin was insignificantly more effective than Levetireacetam in controlling status epilepticus in children.

No serious side effects were reported in Levetireacetam or Phenytoin group.

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10/17/2020