Outcome of Intravenous Levetiracetam Versus Intravenous Phenytoin in Management of Children with Status Epilepticus"

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ABSTRACT

Objective: To compare the outcome of intravenous Levetiracetam versus intravenous Phenytoin in the management of children with status epilepticus

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Pediatric Medicine, Combined Military Hospital, Kharian, from Jan to Dec 2020.

Methodology: Ninety children fulfilling the inclusion criteria were included in the study from emergency. Then patients were randomly divided into two groups by using the lottery method. In group A, patients were given Phenytoin (20 mg/kg) at presentation. In group B, patients were given Levetiracetam (20 mg/kg). These children were admitted to the pediatric ward and followed up until the resolution of symptoms. Duration of resolution of symptoms was noted. Then children were followed up further for 24 hours. If there was no recurrence of seizures, then it was noted.

Results: The mean duration of resolution of symptoms in Group A and Group B was 22.24 ± 3.85 and 16.40 ± 4.50 seconds, respectively. No significant difference was seen in both treatment groups regarding recurrence, i.e., Group-A: 5 (11.1%) vs Group-B: 7 (15.6%), *p*-value=0.932.

Conclusion: Based on the results of this study, it can be concluded that with Levetiracetam, the resolution of symptoms was faster than with Phenytoin. But recurrence rate showed no significant difference in children with status epilepticus.

Keywords: Children, Intravenous, Levetiracetam, Management, Outcome, Phenytoin, Status epilepticus.

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INTRODUCTION

One of the most common pediatric emergencies paediatricians see in the emergency department is convulsive status epilepticus (SE).[1] Status epilepticus in children is a significant cause of admissions to pediatric intensive care units with an annual incidence of 20 per 100000.[2] Although status epilepticus has low mortality in children. However, it carries a burden of high morbidity and complications. The rate of complications such as neutralizability, cognitive impairment, learning issues, and drug-resistant epilepsy can be as high as 22%. The frequency of complications is directly proportional to the duration of convulsive status epilepticus.[3]

The diagnosis of status epilepticus is usually straightforward. Generalized tonicclinic jerks, frothing and dysautonomia features with or without loss of consciousness point to the diagnosis of SE. Sometimes the diagnosis of SE can be difficult because there are certain mimickers of SE as well, such as psychogenic SE, subtle writhing and in phase limb movements, and unresponsive behaviour that needs to be differentiated quickly from true SE. On the other hand, non-convulsive status epilepticus can cause serious diagnostic difficulties, and diagnosis must be considered in altered sensorium and coma following seizures. It is recommended to monitor EEG continuously in these cases. Misdiagnosis can cause some severe iatrogenic complications. Video-EEG monitoring is the gold standard to differentiate the mimickers.[4,5]

One of the newer anti-epileptic agents is Leviteracitam. Levetiracetam is effective against various seizures; however, it has not been well studied in cases of SE.[6] Phenytoin is not an ideal drug in SE. Phenytoin is not only associated with certain severe adverse effects such as liver dysfunction, bone marrow suppression and rashes such as Stevens-Johnson Syndrome, but it is also a hepatic enzyme inducer and affects other anti-epileptic drugs levels.[7,8] It has been reported that Levetiracetam may be a better alternative to Phenytoin.[9,10]

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The rationale of the study was to compare the outcome of intravenous Levetiracetam versus intravenous Phenytoin in the management of children with SE. Literature has reported varied data regarding the outcome of intravenous Levetiracetam versus intravenous Phenytoin for managing children with SE. Moreover, there is no local literature available in this regard, which could help us get evidence regarding a more efficacious drug for SE. So, we want to conduct this study to confirm the evidence and get a more beneficial and efficacious therapy for managing SE in children belonging to the local population. In addition, this will help improve our knowledge and update guidelines in the future for the treatment of SE in children.

METHODOLOGY

This quasi-experimental study was carried out in the Department of Pediatric Medicine, Combined Military Hospital, Kharian, from January to December 2020. The sample size of 90 children, 45 in each group, was calculated with a 95% confidence level, 80% power of the study and taking the magnitude of mean duration for resolution of symptoms, i.e., 22 ± 10 min with Phenytoin & 17 ± 6.25 min with intravenous Levetiracetam for treatment of SE.11 The sampling technique used was non-Probability consecutive sampling.

Inclusion criteria: Children of either gender and age 2-15years, with SE were included in the study.

Exclusion criteria: Children with liver disorders (ALT or AST >40IU, bilirubin >17 mIU), renal disease (creatinine >1.2 mg/dl), and cardiac disease (on medical record) and children with altered sensorium without clinically evident seizures (on medical record) were excluded from the study.

Status epilepticus was defined as prolonged or recurrent seizure activity without returning to baseline and lasting more than 5 minutes.12 The outcome was measured in the following: Duration of resolution of symptoms was measured in minutes required to resolve convulsions and stay calm. Recurrence was labelled if there were convulsions within 24 hours after administering medicines. We hypothesised that there is a difference in the outcome of Levetiracetam versus Phenytoin in the treatment of children with SE. After taking approval of the institutional review board and ethical committee, 90 children were included in the study from the emergency Pediatric Department, Combined Military Hospital, Kharian. Informed consent was taken from parents. Demographic details (name, age, gender, duration of symptoms) were noted. Then patients were randomly divided into two groups by using the lottery method. In group A, patients were given Phenytoin (20 mg/kg) at presen-tation. In group B, patients were given Levetiracetam (20 mg/kg). Then children will be admitted to the pediatric ward and followed up until the resolution of symptoms. Duration of resolution of symptoms was noted. Then children were followed up further for 24 hours. If there was no recurrence of seizures, it was noted (as per operational definition).

Data collected on proforma were analyzed on the statistical package for social sciences version 24.0. Quantitative variables were presented by Mean ± SD. Qualitative variables were presented by frequency and percentage. Both groups were compared using the chi-square test for recurrence within 24 hours and using independent samples t-test for the mean duration of resolution of symptoms. The *p*-value of ≤0.05 was considered significant.

RESULTS

The total number of patients included in the study was 90; 45 in group A and 45 in group B. Mean age of patients in Group-A and Group-B was 8.88 ± 4.14 and 8.31 ± 4.62 years, respectively. In Group-A, 25 (55.6%) patients were male, and 20 (44.6%) were female, while in Group-B, 21 (46.7%) were male, and 24 (53.3%) were female. The mean duration of resolution of symptoms in Group-A and Group-B was 22.24 ± 3.85 minutes and 16.40 ± 4.50 minutes, respectively. No significant difference was seen in both treatment groups regarding recurrence. i.e., Group-A: 5 (11.1%) vs. Group-B: 7 (15.6%), *p*-value=0.932. The mean mRS score in Group-A and Group-B was 1.84 ± 1.33 and 2.11 ± 1.51, respectively. Although the frequency of good outcomes was higher in Group-B patients, it was not statistically significant. i.e., Group-A: 5 (11.1%) vs. Group-B: 7 (15.6%), *p*-value=0.334.

Recurrence of symptoms within 24 hours was stratified for age and gender. Patients were divided into two age groups; 2-8 years and 9-15 years. The age of children did not show a significant association with recurrence in both treatment groups. i.e. 2-8 years (*p*-value) =0.672 and 9-15 years (*p*-value)= 0.089 (Table-I).

Table-I: Recurrence in treatment groups with respect to age.

Age Groups		Group-A Phenytoin	Group-B Levetiracetam	*p*-value
2-8 Years	Yes	3 (12%)	2 (8.3%)	0.672
	No	22 (88%)	22 (91.7%)	
9-15 Years	Yes	1 (5%)	5 (23.8%)	0.240
	No	18 (90%)	16 (76.2%)	

No significant difference was seen in recurrence among male and female children in both treatment groups. i.e., Male (*p*-value) =0.507 and Female (*p*-value) =0.389 (Table-II).

Table-II: Recurrence in treatment groups with respect to gender.

Gender		Group-A Phenytoin	Group-B Levetiracetam	*p*-value
Male	Yes	4 (16%)	4 (19%)	0.786
	No	21 (84%)	17 (81%)	
Female	Yes	1 (5.0%)	3 (12.5%)	0.389
	No	19 (95.0%)	21 (87.5%)	

Similarly, the resolution of symptoms in minutes was cross-tabulated for age groups and gender. Duration of symptoms was significantly higher in Group-A patients in both age groups. i.e., 2-8 years (*p*-value <0.001) and 9-15 years (*p*-value<0.001) (Table-III).

Table-III: Duration of resolution (In Minutes) of symptoms in treatment groups with respect to age groups.

Age Groups	Group-A Phenytoin	Group-B Levetiracetam	*p*-value
2-8 Years	22.48 ± 3.82	17.54 ± 4.62	<0.001
9-15 Years	21.95 ± 3.96	15.09 ± 4.09	<0.001

For male and female children mean duration of resolution of symptoms was significantly higher for Group-A patients (Table-IV).

Table-IV: Duration of resolution (In Minutes) of symptoms in treatment groups with respect to gender.

Gender	Group-A Phenytoin	Group-B Levetiracetam	*p*-value
Male	22.16 ± 4.21	16.19 ± 4.15	0.001
Female	22.35 ± 3.43	16.58 ± 4.88	0.001

DISCUSSION

SE requires urgent medical intervention in the emergency department. SE affects children commonly compared to adults with comparable frequency in both males and females. It may be the first presentation of epilepsy in children. SE and carries a high burden of morbidity and mortality despite advancements in neuro pharmaceuticals. Prolonged and uncontrolled seizures can permanently damage the brain and result in cognitive impairment and developmental regression. This situation can be avoided by an aggressive multidisciplinary approach to ineffective seizure management in SE.[9]

Phenytoin is the recommended second-line intravenous anticonvulsant for the treatment of pediatric convulsive SE; however, some evidence suggests that a newer anticonvulsant, Levetiracetam, can be administered quickly has a good safety profile.[10] In this study, we compared the outcome of Levetiracetam versus Phenytoin in the treatment of children with SE. Literature has reported varied data regarding the outcome of Levetiracetam versus Phenytoin for the management of children with SE. Moreover, there is no homegrown literature available in this regard, which could aid us in getting the evidence regarding a more efficacious drug for SE. This study showed that the duration of resolution of symptoms was significantly lower with Levetiracetam compared to Phenytoin. i.e., 16.40 ± 4.50 sec vs 22.24 ± 3.85 sec, *p*-value=0.000. However, results regarding recurrence showed no difference between the two drugs. i.e., Phenytoin: 11.1% & Levetiracetam: 15.6%, *p*-value=0.334.

Three randomized controlled trials from the subcontinent region show the superior efficacy of intravenous Levetiracetam as compared to Phenytoin for the treatment of SE in children (92.7% vs 83.3%, 96% vs 59.6%, and 91.2% vs 85.6%, respectively).[8,11,12]

However, other trials in adults and paediatrics have failed to show a significant difference between these two drugs in aborting the SE within 24 hours.[6,13,14]

There is insufficient data in adults and paediatrics to recommend the use of Levetiracetam as initial or second-line therapy. Insufficient data exist in adults about the efficacy of LEV as either initial or second therapy (level U)", and "insufficient data exist in children regarding the efficacy of phenytoin or LEV as second therapy after failure of a benzodiazepine (level U)".[15] Only a class III randomized controlled trial supported the of LEV in treatment of SE in children. This study found equal efficacy of lorazepam (76.3%) and LEV 20 mg/kg (75.6%). AES guidelines recommend a class I trial to improve the level of evidence in favour of LEV as first-line therapy.[15]

The EcLiPSE trial (class II) compared the use of LEV at 40 mg/kg and Phenytoin at 20 mg/kg in 286 children as a second-line agent after the initial dose of lorazepam. This trial showed improved efficacy and a better adverse effect profile of LEV than Phenytoin.[16] The ConSEPT trial (class II) in Australia and New Zealand also compared both drugs as a second-line agents. The trial also concluded better efficacy and adverse effect profile of LEV. Clinical cessation of convulsive SE 5 minutes after the completion of the loading dose occurred in 50% of children in the Phenytoin group and 60% in the LEV group (*p*-value=0.16).[7] Gujjar *et al,* also found similar efficacy of LEV and

Phenytoin (82% vs 70%, respectively; *p*-value =0.33).[17] An Indian retrospective study shows 90 % efficacy of LEV.[18] Another study reported that 89% of patients were seizure-free within one hour of adminis-tration of Levetiracetam.[19]

Phenytoin efficacy is well established in children. LEV is currently being used in adults and paediatric patients due to a better adverse effect profile. Phenytoin has got certain serious adverse effects that have led to the search for an alternative safe agent to treat status epilepticus.

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CONCLUSION

Based on this study, it can be concluded that, as with Levetiracetam, the resolution of symptoms was faster than with Phenytoin. Nevertheless, the recurrence rate showed no significant difference in children with SE. Therefore, considering the faster seizure resolution and better adverse effect profile of Levetirecitam compared to Phenytoin, we recommend that it be used as a first-line agent in SE in children.

Conflict of Interest: None.

Authors' Contribution

SZ: Original research, AS: Assistance in research, SAS: Article writing, MZ: Literature review, QUZK: Data collection, MM: Help in article submission.

REFRENCES

1. Lyttle MD, Rainford NE, Gamble C. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet 2019; 393(10186): 2125-2134.
2. Gaínza-Lein M, Fernández IS, Ulate-Campos A. Timing in the treatment of status epilepticus: From basics to the clinic. Seizure 2019; 68(1): 22-30.
3. Lyttle MD, Gamble C, Messahel S. Emergency treatment with levetiracetam or phenytoin in status epilepticus in children-the EcLiPSE study: study protocol for a randomised controlled trial. Trials 2017; 18(1): 1-10.
4. Jaramillo-Jiménez E, Vargas-García C, Rodríguez-Márquez I. Psychogenic non-epileptic and epileptic seizures: clues for a differential diagnosis. Findings from a Colombian study. Rev Neurol 2019; 69(4): 145-151.
5. Krogstad MH, Høgenhaven H, Beier CP. Nonconvulsive status epilepticus: validating the Salzburg criteria against an expert EEG examiner. J Clin Neurophysiol 2019; 36(2): 141-145.
6. 6.Lyttle MD, Rainford NE, Gamble C. Levetiracetam versus pheny-toin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet 2019; 393(10186): 2125-2134.
7. Dalziel SR, Borland ML, Furyk J. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicenter, randomised controlled trial. Lancet 2019; 393(10186): 2135-2145.
8. 8.Noureen N, Khan S, Khursheed A. Clinical efficacy and safety of injectable levetiracetam versus phenytoin as second-line therapy in the management of generalized convulsive status epilepticus in children: an open-label randomized controlled trial. J Clin Neurol 2019; 15(4): 468-472.
9. Kazmi A, Abbas G, Khurshid A. A comparison of intravenous midazolam and diazepam in management of status epilepticus in children. J Pak Med Assoc 2021; 71(2): 640-644.
10. Angurana SK, Suthar R. Efficacy and Safety of Levetiracetam vs. Phenytoin as Second Line Antiseizure Medication for Pediatric Convulsive Status Epilepticus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Trop Pediatr 2021; 67(2): fmab014.
11. Sharma P, Mandot S, Bamnawat S. Levetiracetam versus phenytoin for treatment of convulsive status epilepticus in pediatric population: a randomized controlled trial. Int J Contemp Pediatr 2019; 6(2): 741.
12. Wani G, Imran A, Dhawan N. Levetiracetam versus phenytoin in children with status epilepticus. J Family Med Prim Care 2019; 8(10): 3367-3371.
13. Nakamura K, Inokuchi R, Daidoji H. Efficacy of levetiracetam versus fosphenytoin for the recurrence of seizures after status epilepticus. Medicine (Baltimore) 2017; 96(25): e7206.
14. Singh K, Aggarwal A, Faridi MMA. IV Levetiracetam versus IV Phenytoin in Childhood Seizures: A Randomized Controlled Trial. J Pediatr Neurosci 2018; 13(2): 158-164.
15. Glauser T, Shinnar S, Gloss D. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr 2016; 16(1): 48-61.
16. Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study. J Neurol 2012; 259(4): 645-648.
17. Gujjar AR, Nandhagopal R, Jacob PC. Intravenous levetiracetam vs phenytoin for status epilepticus and cluster seizures: a prospective, randomized study. Seizure 2017; 49(1): 8-12.
18. Goraya JS, Khurana DS, Valencia I. Intravenous levetiracetam in children with epilepsy. Pediatr Neurol 2008; 38(3): 177-180.
19. Ng YT. Intravenous levetiracetam in children with seizures: a prospective safety study. J Child Neurol 2010; 25(5): 551-555.