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Efficacy and Safety of Levetiracetam Versus Fosphenytoin in Adult Convulsive Status Epilepticus: An Open-Label Randomized Controlled Trial

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Abstract

Background

Convulsive status epilepticus is a time-critical neurological emergency, and the choice of second-line intravenous antiseizure medication in resource-limited hospitals rests on habit rather than on local evidence. We compared intravenous levetiracetam with intravenous fosphenytoin in adults whose convulsive status epilepticus persisted after intravenous diazepam.

Methods

This single-center, open-label, parallel-group randomized controlled trial was conducted in the Department of Neurology of Dhaka Medical College Hospital, Dhaka, Bangladesh, from May 2023 to August 2024. A total of 62 adults aged 18 years or older who continued to convulse 15 minutes after intravenous diazepam 10 mg were allocated in a 1:1 ratio by block randomization to fosphenytoin 20 mg per kg phenytoin sodium equivalent or levetiracetam 60 mg per kg. The primary efficacy endpoint, on which the sample size was based, was cessation of clinically apparent seizures within 30 minutes of starting the trial drug without any additional anticonvulsant. Sustained seizure control to 24 hours and treatment emergent adverse events at 24 hours, which together formed the registered primary outcome, were also assessed. Secondary outcomes included time to seizure termination, recurrence within 24 hours, treatment emergent adverse events, intensive care admission, endotracheal intubation, length of hospital stay, all-cause in-hospital mortality, modified Rankin Scale score at seven days or discharge, and total drug cost.

Results

Seizure cessation within 30 minutes was achieved in 16 of 31 patients (51.6%) given fosphenytoin and 20 of 31 patients (64.5%) given levetiracetam, an absolute difference of 12.9% (95% CI: −11.5 to 37.3; p = 0.303). Seizure control sustained to 24 hours, the efficacy component of the registered primary outcome, was achieved in 38.7% and 48.4%, respectively (p = 0.442). Among responders, convulsions stopped at a median of 13.5 minutes with fosphenytoin and 11.0 minutes with levetiracetam (p = 0.034). Recurrence within 24 hours was similar (12.9% with fosphenytoin and 16.1% with levetiracetam; p = 1.000), but the mean seizure-free interval before recurrence was longer with levetiracetam (229.2 versus 92.5 minutes; p = 0.045). Treatment emergent adverse events at 24 hours were less frequent with levetiracetam than with fosphenytoin (38.7% versus 71.0%; p = 0.011), with lower rates of sedation, itching, and rash. Intensive care admission, intubation within 24 hours, length of hospital stay, in-hospital mortality (6.5% with fosphenytoin and 9.7% with levetiracetam; p = 1.000), modified Rankin Scale distribution at seven days or discharge, and total drug cost (median 1272 taka with fosphenytoin and 1100 taka with levetiracetam; p = 0.137) were comparable between the groups. The same molecule was continued as oral maintenance therapy in 78.6% of levetiracetam recipients compared with 13.8% of fosphenytoin recipients (p < 0.001).

Conclusions

No statistically significant difference was found between levetiracetam and fosphenytoin in stopping benzodiazepine refractory convulsive status epilepticus in adults, although this small open-label trial cannot establish equivalence. Levetiracetam was better tolerated at 24 hours, cost no more, and simplified the transition to oral therapy, which makes it a reasonable second-line option for hospitals with limited monitoring and critical care capacity while larger blinded trials are awaited.

Categories: Neurology, Pharmacology, Emergency Medicine

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Keywords: antiseizure medication, bangladesh, fosphenytoin, levetiracetam, randomized controlled trial, status epilepticus

Introduction

Epilepsy is among the most common serious neurological disorders and affects more than 50 million people worldwide [1]. Close to 80% of them live in low- and middle-income countries, where the epilepsy treatment gap has narrowed only slowly and still leaves most patients in the poorest settings untreated [2]. A national household survey placed the prevalence of epilepsy in Bangladesh at 8.4 per 1000 population, which places well over a million people at risk of a seizure emergency [3].

Status epilepticus is that emergency. The International League Against Epilepsy defines it as a condition arising from failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizures, and it fixes five minutes of continuous convulsion as the point at which emergency treatment must begin [4]. The condition is neither rare nor benign. Nationwide data show a rising incidence and a case fatality that remains close to one death in five, and outcome deteriorates steeply with every additional minute of uncontrolled convulsive activity [5,6]. Older adults and those patients who go on to develop refractory disease fare worst of all [7,8].

Intravenous benzodiazepines are the accepted first-line treatment, yet they fail in roughly one-third to one-half of patients, and every failure forces an immediate choice of a second-line intravenous antiseizure medication [9,10]. That choice carries unusual weight, because the window during which drugs still work closes rapidly and each unsuccessful agent consumes another 30 minutes of ongoing cerebral injury [11].

Fosphenytoin has long been the conventional second-line agent in Bangladeshi hospitals. It is effective, but it must be infused slowly under blood pressure and rhythm surveillance because it can precipitate hypotension, bradyarrhythmia, and asystole and it carries a well-described burden of skin hypersensitivity [12]. Levetiracetam acts through synaptic vesicle glycoprotein 2A, has negligible hepatic enzyme interactions, and can be delivered rapidly without cardiac monitoring [13].

Three large randomized trials and several meta-analyses have compared these two drugs and have consistently failed to separate them on the ability to stop seizures [14-20]. Almost all of that evidence comes from health systems in which convulsions are treated by paramedics within the first hour, cardiac monitoring during infusion is routine, and an intensive care bed with a ventilator is available when the airway fails. Patients in Bangladesh reach a tertiary hospital far later, monitoring is frequently intermittent, ventilators are scarce, and families buy every ampoule from their own pocket [21,22]. Under these conditions, a drug with a wider cardiovascular safety margin and a simpler infusion protocol may be worth considerably more than equivalence trials from wealthy settings imply, whereas a drug that families cannot afford is worth nothing at all. Safety and affordability are therefore not secondary endpoints. They decide whether a drug can be used at all.

No randomized comparison of levetiracetam and fosphenytoin has ever been reported from Bangladesh. Prescribing rests on habit, on whichever ampoule the pharmacy holds that night, and on an untested assumption that levetiracetam costs more. Clinicians thus make a time-critical bedside decision with no local evidence at all, in the setting where a wrong decision is hardest to reverse. We therefore conducted an open-label randomized controlled trial at Dhaka Medical College Hospital to compare the efficacy, safety, functional outcome, and treatment cost of intravenous levetiracetam and intravenous fosphenytoin in adults whose convulsive status epilepticus persisted after intravenous diazepam. The primary objective was to compare the proportion of patients in whom clinically apparent seizures stopped within 30 minutes of starting the trial drug. The secondary objectives were to compare seizure control and treatment emergent adverse events at 24 hours, which together formed the registered primary outcome, as well as the time to seizure termination, seizure recurrence, the need for intensive care and intubation, in-hospital mortality, functional outcome, and drug cost.

Materials And Methods

Study design and setting

This was a single-center, open-label, parallel-group randomized controlled trial with a 1:1 allocation, conducted in the Department of Neurology of Dhaka Medical College Hospital, a public tertiary care teaching hospital in Dhaka, Bangladesh, between May 2023 and August 2024. The trial is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement [23].

Participants

Consecutive adults aged 18 years or older who were admitted with convulsive status epilepticus, diagnosed according to the 2015 criteria of the International League Against Epilepsy Task Force [4], were assessed for eligibility. Patients were excluded if they had already been intubated before treatment, if the acute precipitant was major trauma, hypoglycemia, hyperglycemia, cardiac arrest, or an anoxic insult, if they had a

known allergy to either trial drug, if they were pregnant or lactating, if the presentation was non-convulsive status epilepticus, or if they had renal failure, hepatic failure, or established cardiovascular disease. Written informed consent was obtained from the patient or from a legal attendant before enrollment.

Randomization and blinding

Every patient first received intravenous diazepam 10 mg. Patients who continued to convulse 15 minutes later were randomly assigned in a 1:1 ratio using permuted blocks of six, which gave 11 blocks for the planned sample. Within each block, the first, third, and fifth allocations were drawn by lottery, and the remaining allocations received the alternative drug. The allocation sequence was not generated in advance. Instead, the lottery for each odd-numbered position was drawn by the enrolling physician at the bedside only after eligibility had been confirmed and consent obtained, so the assignment of these patients could not be foreseen. Each even-numbered position, however, followed directly from the preceding draw, and no additional concealment method, such as sequentially numbered opaque sealed envelopes or central allocation, was used, so the assignment of these patients could have been anticipated by the enrolling team. In total, 62 adults were randomly assigned, 31 to fosphenytoin and 31 to levetiracetam. All of them received the allocated treatment and were followed to seven days or hospital discharge, with no loss to follow-up (Figure *1*). The trial was open label, and neither participants, treating clinicians, nor outcome assessors were masked to the assignment.

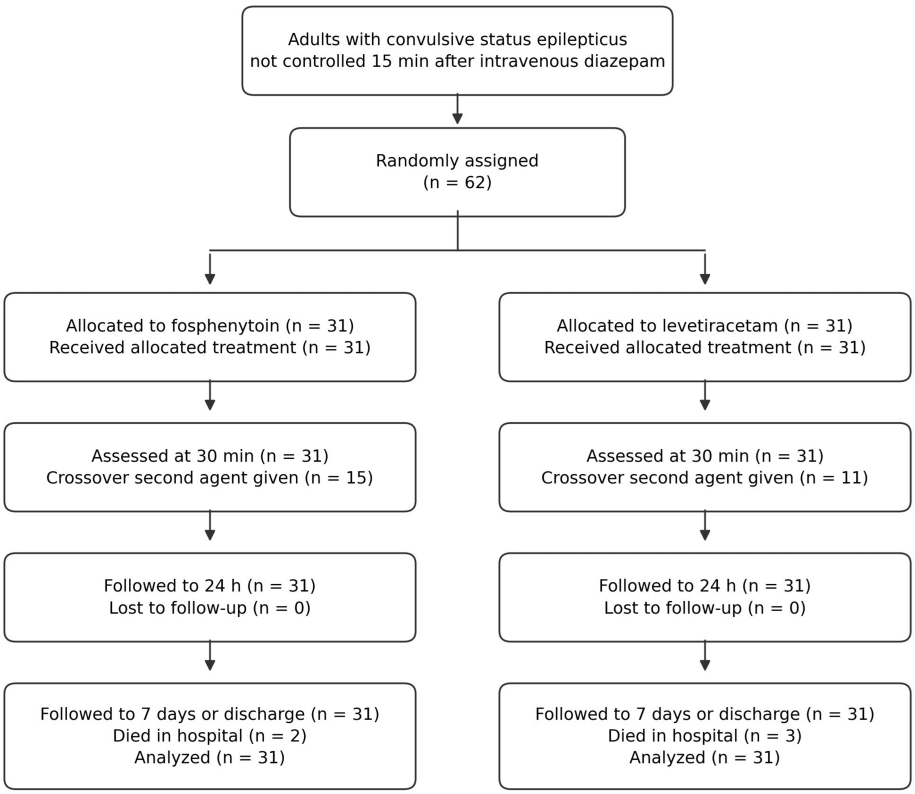


FIGURE 1: Patients' allocation

Interventions

Resuscitation, airway protection, oxygen supplementation, venous access, and blood pressure support were carried out in parallel with drug administration in every patient. Patients allocated to fosphenytoin received 20 mg per kg phenytoin sodium equivalent, to a maximum of 1500 mg phenytoin equivalent, diluted in 40 mL of normal saline and infused at a rate not exceeding 3 mg per kg per minute or 150 mg per minute. Patients allocated to levetiracetam received 60 mg per kg, to a maximum of 4500 mg, diluted in 25 mL of normal saline and infused over 10 minutes.

Patients were reassessed 30 minutes after the start of the trial drug infusion. If convulsions persisted, the alternative study drug was given at the same dose as a crossover second agent. Patients whose seizures continued for a further 30 minutes were transferred to the intensive care unit for third-line anesthetic therapy with propofol, thiopental sodium, or midazolam according to unit protocol. Once status epilepticus was controlled, maintenance therapy was given as fosphenytoin 300 mg intravenously daily in two divided doses or levetiracetam 1000-1500 mg intravenously daily in two or three divided doses, and the subsequent

oral antiseizure medication was selected on the basis of seizure semiology, etiology, electroencephalographic findings, and patient age. Investigations included complete blood count, blood glucose, serum electrolytes, calcium, magnesium, urea, creatinine, liver function tests, electroencephalography, and computed tomography or magnetic resonance imaging of the brain as clinically indicated.

Outcomes

The primary efficacy endpoint was cessation of clinically apparent seizures within 30 minutes of the start of the trial drug infusion without the administration of any additional anticonvulsant. Cessation was not credited if convulsions continued, if they recurred within 30 minutes, or if third-line treatment was started within 30 minutes [14,24]. Clinically apparent seizure was defined as visually observed focal or generalized tonic-clonic movement, nystagmoid or rhythmic eye movement, or generalized or segmental myoclonus.

Secondary outcomes were the time from the start of infusion to the termination of convulsions among patients with treatment success, seizure recurrence between 30 minutes and 24 hours, the seizure-free interval preceding recurrence, use of and response to the crossover agent, treatment emergent adverse events at 30 minutes, 24 hours, and seven days or discharge, intensive care admission, endotracheal intubation within 24 hours, length of intensive care and hospital stay, all-cause in-hospital mortality, transition to an oral antiseizure medication, the modified Rankin Scale score [25,26] at seven days or discharge, and the total cost of the trial drug over the treatment episode. Adverse event severity was graded with the Division of AIDS table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 [27]. Patients were assessed at 30 minutes, at 24 hours, and at seven days or hospital discharge, whichever came first.

Registered and reported outcomes

The trial registration (NCT06403150) named as its primary outcome the efficacy and safety of the two drugs at 24 hours, described as seizure control after drug initiation and the incidence of treatment emergent adverse events, and listed seizure cessation within 30 minutes among its secondary outcomes. The sample size, however, had been calculated from the expected rate of seizure cessation within 30 minutes, so this is the only endpoint for which the trial had a planned statistical basis, and it is therefore presented in this report as the primary efficacy endpoint. To keep the registered primary outcome fully visible, both of its components are reported in their own right and are marked in the tables below. The efficacy component is reported as sustained seizure control to 24 hours, defined as seizure cessation within 30 minutes without recurrence up to 24 hours, together with its two elements, seizure cessation and seizure recurrence within 24 hours. The safety component is reported as any treatment emergent adverse event at 24 hours. The remaining registered secondary outcomes, namely, seizure recurrence within 24 hours, adverse events at 30 minutes, 24 hours, and discharge, intubation within 24 hours, all-cause in-hospital mortality, and the modified Rankin Scale score, are all reported. The registry listed a time frame of 30 days for mortality and assessment of the modified Rankin Scale score at 30 minutes, 24 hours, and discharge, whereas follow-up in this trial ended at seven days or hospital discharge, so mortality is reported for the index admission and the modified Rankin Scale score at seven days or discharge, whichever came first. The registry also described recurrence as a clinically apparent seizure or a non-convulsive seizure detected by electroencephalography, but because electroencephalography was not performed routinely, recurrence is reported on clinical grounds only. Time to seizure termination, the seizure-free interval before recurrence, use of and response to the crossover agent, intensive care admission, length of intensive care and hospital stay, transition to an oral antiseizure medication, and drug cost were not listed in the registry and are reported as exploratory outcomes.

Sample size

The sample size was calculated for a noninferiority comparison, assuming a response rate of 80% for the reference treatment [16], a two-sided alpha of 0.05, a power of 80%, and a noninferiority margin of 0.30, which required 28 patients per group. Allowing 10% for attrition, 31 patients were recruited into each arm. With this margin, noninferiority of levetiracetam would be supported if the lower limit of the two-sided 95% confidence interval (CI) for the difference in response, levetiracetam minus fosphenytoin, lay above −30 percentage points. The trial was not designed or powered to show equivalence or superiority.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, V. 25.0 (IBM Corp., Armonk, NY, USA). Normality was examined with the Shapiro-Wilk test. Normally distributed continuous variables are presented as mean with standard deviation and were compared with the independent samples t-test, and variables that were not normally distributed are presented as median with interquartile range and were compared with the Mann-Whitney U test. Categorical variables are presented as frequency with percentage and were compared with the Pearson chi-squared test, with Fisher's exact test substituted whenever an expected cell count fell below five. The absolute difference in the primary outcome is reported with a 95% CI based on the normal approximation. The same method was used for sustained seizure control to 24 hours. All analyses followed the intention-to-treat principle, and because every randomized patient received the allocated drug and

completed follow-up, the intention-to-treat and per-protocol populations were identical. No adjustment was made for multiple comparisons, so secondary and exploratory outcomes are interpreted as hypothesis-generating. A two-sided p-value below 0.05 was considered statistically significant.

Ethical consideration

The protocol was approved by the Ethical Review Committee of Dhaka Medical College (approval number: ERC-DMC/ECC/2023/131). The trial was registered at ClinicalTrials.gov (NCT06403150). Written informed consent was obtained from every participant or from a legally authorized representative before enrollment. All procedures were carried out in accordance with the Declaration of Helsinki.

Results

The mean age of the participants was 40.65 (SD: 18.47) years in the fosphenytoin group and 44.03 (SD: 18.14) years in the levetiracetam group ($t(60) = 0.73$; $p = 0.469$), and men predominated in both arms (64.5% and 74.2%; $\chi^2(1) = 0.68$; $p = 0.409$). Generalized tonic-clonic status epilepticus was the commonest presentation (71.0% and 77.4%), and the leading causes were idiopathic or undetermined (25.8% and 32.3%) and old stroke (29.0% and 25.8%). The median seizure duration before enrollment was 100 minutes (IQR: 90 to 120) with fosphenytoin and 110 minutes (IQR: 100 to 130) with levetiracetam ($Z = 1.82$; $p = 0.069$), and a benzodiazepine had been administered before arrival in 58.1% and 67.7%, respectively. The two groups did not differ significantly on any baseline demographic, comorbid, or disease-related variable (Table *1*).

Characteristic	Fosphenytoin (n = 31)	Levetiracetam (n = 31)	Test statistic	P-value
Age, years, mean (SD)	40.65 (18.47)	44.03 (18.14)	t(60) = 0.73	0.469[b]
Age group, years				
18 to 30	11 (35.5)	9 (29.0)	$\chi^2(5) = 2.09$	0.836
31 to 40	8 (25.8)	5 (16.1)		
41 to 50	5 (16.1)	7 (22.6)		
51 to 60	2 (6.5)	4 (12.9)		
61 to 70	2 (6.5)	3 (9.7)		
71 to 80	3 (9.7)	3 (9.7)		
Sex				
Male	20 (64.5)	23 (74.2)	$\chi^2(1) = 0.68$	0.409
Female	11 (35.5)	8 (25.8)		
Residence				
Urban	20 (64.5)	19 (61.3)	$\chi^2(1) = 0.07$	0.793
Rural	11 (35.5)	12 (38.7)		
Educational level				
Illiterate	6 (19.4)	5 (16.1)	$\chi^2(4) = 1.23$	0.873
Primary	13 (41.9)	10 (32.3)		
Secondary	7 (22.6)	9 (29.0)		
Higher secondary	3 (9.7)	5 (16.1)		
Graduate or above	2 (6.5)	2 (6.5)		
Occupation				
Home maker	9 (29.0)	7 (22.6)	$\chi^2(5) = 1.98$	0.852
Student	7 (22.6)	5 (16.1)		
Day laborer, farmer, or rickshaw puller	5 (16.1)	5 (16.1)		
Service holder	4 (12.9)	4 (12.9)		

Unemployed	4 (12.9)	5 (16.1)		
Business	2 (6.5)	5 (16.1)		
Comorbidities				
Hypertension	4 (12.9)	7 (22.6)	$\chi^2(1) = 0.99$	0.319
Diabetes mellitus	3 (9.7)	6 (19.4)	NA	0.473[a]
Dyslipidemia	9 (29.0)	8 (25.8)	$\chi^2(1) = 0.08$	0.776
Hypothyroidism	1 (3.2)	1 (3.2)	NA	1.000[a]
Previous diagnosis of epilepsy	21 (67.7)	19 (61.3)	$\chi^2(1) = 0.28$	0.596
Family history of epilepsy	3 (9.7)	2 (6.5)	NA	1.000[a]
Past febrile seizure	3 (9.7)	4 (12.9)	NA	1.000[a]
Type of convulsive status epilepticus				
Generalized tonic-clonic	22 (71.0)	24 (77.4)		
Focal onset evolving to bilateral convulsive	5 (16.1)	5 (16.1)	$\chi^2(2) = 0.75$	0.686
Focal motor	4 (12.9)	2 (6.5)		
Cause of status epilepticus				
Idiopathic or undetermined	8 (25.8)	10 (32.3)		
Old stroke	9 (29.0)	8 (25.8)		
Central nervous system infection	5 (16.1)	4 (12.9)		
Other causes	7 (22.6)	5 (16.1)	$\chi^2(5) = 1.39$	0.925
Old head trauma	1 (3.2)	2 (6.5)		
Brain neoplasm	1 (3.2)	2 (6.5)		
Seizure duration at enrollment, minutes, median (IQR)	100 (90 to 120)	110 (100 to 130)	Z = 1.82	0.069[c]
Benzodiazepine given before arrival	18 (58.1)	21 (67.7)	$\chi^2(1) = 0.62$	0.430

TABLE 1: Baseline demographic and clinical characteristics of the two treatment groups

Values are presented as n (%) unless otherwise stated.

[a]Fisher's exact test. [b]Independent samples t-test. [c]Mann-Whitney U test.

All other p-values are from the Pearson chi-squared test. Test statistics are the Pearson chi-squared value with degrees of freedom (χ^2), the independent samples t value with degrees of freedom (t), and the standardized Mann-Whitney U value (Z); absolute values of t and Z are shown. NA, not applicable, because Fisher's exact test does not produce a test statistic.

IQR: interquartile range; SD: standard deviation

The primary efficacy endpoint was achieved in 16 of 31 patients (51.6%) given fosphenytoin and 20 of 31 patients (64.5%) given levetiracetam, an absolute difference of 12.9% in favor of levetiracetam (95% CI: −11.5 to 37.3; $\chi^2(1) = 1.06$; p = 0.303). The lower limit of this interval lay above the noninferiority margin of −30 percentage points, but the interval was wide and remained compatible with a difference of 11.5 percentage points in favor of fosphenytoin as well as one of 37.3 percentage points in favor of levetiracetam. Sustained seizure control to 24 hours, the efficacy component of the registered primary outcome, was achieved in 12 patients (38.7%) given fosphenytoin and 15 patients (48.4%) given levetiracetam, an absolute difference of 9.7% (95% CI: −14.9 to 34.2; $\chi^2(1) = 0.59$; p = 0.442). Among patients in whom the trial drug succeeded, the median time from the start of infusion to the termination of convulsions was 13.5 minutes (IQR: 12.2 to 15.8; n = 16) with fosphenytoin and 11.0 minutes (IQR: 9.0 to 15.0; n = 19) with levetiracetam (Z = 2.12; p = 0.034), although the infusion time was not recorded for one levetiracetam responder. Seizures recurred between 30 minutes and 24 hours in four patients (12.9%) given fosphenytoin and five patients (16.1%) given levetiracetam (p = 1.000), but the mean seizure-free interval preceding recurrence was 92.5

(SD: 51.1) minutes and 229.2 (SD: 101.6) minutes, respectively (t(7) = 2.43; p = 0.045). A crossover second agent was required in 15 patients (48.4%) and 11 patients (35.5%), respectively ($\chi^2(1) = 1.06$; p = 0.303), and controlled the seizure in six patients in each arm. Almost all survivors were switched to an oral antiseizure medication, but the same molecule was continued in only four of 29 patients (13.8%) in the fosphenytoin arm compared with 22 of 28 patients (78.6%) in the levetiracetam arm ($\chi^2(1) = 24.10$; p < 0.001) (Table 2).

Outcome	Fosphenytoin (n = 31)	Levetiracetam (n = 31)	Test statistic	P-value
Seizure cessation within 30 minutes (primary efficacy endpoint)	16 (51.6)	20 (64.5)	$\chi^2(1) = 1.06$	0.303
Time to seizure termination among responders, minutes, median (IQR)	13.5 (12.2 to 15.8)	11.0 (9.0 to 15.0)	Z = 2.12	0.034[d]
Seizure recurrence within 24 hours	4 (12.9)	5 (16.1)	NA	1.000[b]
Sustained seizure control to 24 hours[a]	12 (38.7)	15 (48.4)	$\chi^2(1) = 0.59$	0.442
Seizure-free interval before recurrence, minutes, mean (SD)	92.50 (51.07)	229.20 (101.60)	t(7) = 2.43	0.045[c]
Crossover second agent required	15 (48.4)	11 (35.5)	$\chi^2(1) = 1.06$	0.303
Seizure controlled by crossover agent	6 (19.4)	6 (19.4)	$\chi^2(1) = 0.00$	1.000
Time to control with crossover agent, minutes, median (IQR)	43.0 (38.8 to 51.2)	52.5 (43.8 to 60.0)	Z = 1.38	0.168[d]
Switched to an oral antiseizure medication	29 (93.5)	28 (90.3)	NA	1.000[b]
Same molecule continued orally	4/29 (13.8)	22/28 (78.6)	$\chi^2(1) = 24.10$	<0.001

TABLE 2: Primary and secondary efficacy outcomes by treatment group

Values are presented as n (%) unless otherwise stated. Absolute difference in the primary outcome: 12.9% (95% CI: −11.5 to 37.3). Time to seizure termination was analyzed among patients with treatment success (n = 16 and n = 19; the infusion time was not recorded for one levetiracetam responder). The seizure-free interval was analyzed among the four and five patients with recurrence, and the time to control with the crossover agent was analyzed among the six patients in each arm who responded to it. Denominators for oral continuation of the same molecule are the patients switched to an oral drug.

[a]Efficacy component of the registered primary outcome, defined as seizure cessation within 30 minutes without recurrence up to 24 hours; absolute difference 9.7% (95% CI: −14.9 to 34.2). [b]Fisher's exact test. [c]Independent samples t-test. [d]Mann-Whitney U test.

All other p-values are from the Pearson chi-squared test. Test statistics are the Pearson chi-squared value with degrees of freedom (χ^2), the independent samples t value with degrees of freedom (t), and the standardized Mann-Whitney U value (Z); absolute values of t and Z are shown. NA, not applicable, because Fisher's exact test does not produce a test statistic.

IQR: interquartile range; SD: standard deviation

Treatment emergent adverse events were more frequent with fosphenytoin at every assessment, and the difference reached statistical significance at 24 hours, the safety component of the registered primary outcome, when they were recorded in 22 patients (71.0%) given fosphenytoin and 12 patients (38.7%) given levetiracetam ($\chi^2(1) = 6.51$; p = 0.011). The corresponding proportions were 54.8% and 32.3% at 30 minutes ($\chi^2(1) = 3.21$; p = 0.073) and 41.9% and 32.3% at seven days or discharge ($\chi^2(1) = 0.62$; p = 0.430). Intensive care admission was required in nine patients (29.0%) given fosphenytoin and six patients (19.4%) given levetiracetam ($\chi^2(1) = 0.79$; p = 0.374), and endotracheal intubation within 24 hours was required in five patients (16.1%) and three patients (9.7%), respectively (p = 0.707). The median length of intensive care stay was 32.0 hours (IQR: 24.0 to 45.0) and 39.0 hours (IQR: 33.0 to 55.5) (Z = 0.96; p = 0.339), and the median hospital stay was five days in both arms (Z = 0.72; p = 0.470). All-cause in-hospital mortality was two of 31 (6.5%) and three of 31 (9.7%), respectively (p = 1.000). A modified Rankin Scale score of 0-3 at seven days or discharge was reached by 20 patients (64.5%) given fosphenytoin and 18 patients (58.1%) given levetiracetam ($\chi^2(1) = 0.27$; p = 0.602), and the median score was 2.0 (IQR: 0.0 to 4.0) and 3.0 (IQR: 0.0 to 4.0), respectively (Z = 0.27; p = 0.791). The median total cost of the trial drug across the treatment episode was 1272 taka (IQR: 896 to 1586) with fosphenytoin and 1100 taka (IQR: 782 to 1380) with levetiracetam (Z = 1.49; p = 0.137) (Table 3).

Outcome	Fosphenytoin (n = 31)	Levetiracetam (n = 31)	Test statistic	P-value
Any treatment emergent adverse event at 30 minutes	17 (54.8)	10 (32.3)	$\chi^2(1) = 3.21$	0.073
Any treatment emergent adverse event at 24 hours[a]	22 (71.0)	12 (38.7)	$\chi^2(1) = 6.51$	0.011
Any treatment emergent adverse event at 7 days or discharge	13 (41.9)	10 (32.3)	$\chi^2(1) = 0.62$	0.430
Intensive care unit admission	9 (29.0)	6 (19.4)	$\chi^2(1) = 0.79$	0.374
Endotracheal intubation within 24 hours	5 (16.1)	3 (9.7)	NA	0.707[b]
Length of intensive care stay, hours, median (IQR)	32.0 (24.0 to 45.0)	39.0 (33.0 to 55.5)	Z = 0.96	0.339[c]
Length of hospital stay, days, median (IQR)	5.0 (4.0 to 8.0)	5.0 (4.0 to 7.0)	Z = 0.72	0.470[c]
All-cause in-hospital death	2 (6.5)	3 (9.7)	NA	1.000[b]
Modified Rankin Scale score 0 to 3 at discharge	20 (64.5)	18 (58.1)	$\chi^2(1) = 0.27$	0.602
Modified Rankin Scale score, median (IQR)	2.0 (0.0 to 4.0)	3.0 (0.0 to 4.0)	Z = 0.27	0.791[c]
Total cost of trial drug, BDT, median (IQR)	1272 (896 to 1586)	1100 (782 to 1380)	Z = 1.49	0.137[c]

TABLE 3: Safety, clinical course, functional outcome, and cost by treatment group

Values are presented as n (%) unless otherwise stated. Length of intensive care stay was analyzed among the nine and six patients admitted to intensive care.

[a]Safety component of the registered primary outcome. [b]Fisher's exact test. [c]Mann-Whitney U test. All other p-values are from the Pearson chi-squared test.

Test statistics are the Pearson chi-squared value with degrees of freedom (χ^2) and the standardized Mann-Whitney U value (Z); absolute values of Z are shown. NA, not applicable, because Fisher's exact test does not produce a test statistic.

BDT: Bangladeshi taka; IQR: interquartile range

At 24 hours, the events that distinguished the groups were sedation (29.0% versus 3.2%; $\chi^2(1) = 7.63$; p = 0.006), itching (22.6% versus 0%; p = 0.011), and rash (16.1% versus 0%; p = 0.053). Hypotension and cardiac arrhythmia in the form of atrial fibrillation were each recorded in one fosphenytoin recipient (3.2%) at 30 minutes and in no levetiracetam recipient, while respiratory depression at 30 minutes occurred in three fosphenytoin recipients (9.7%) and two levetiracetam recipients (6.5%). All of these events resolved after the immediate discontinuation of the infusion together with supportive care, and the affected patients were switched to the alternative agent. No episode of anaphylaxis, Stevens-Johnson syndrome, or purple glove syndrome was observed in either arm (Table *4*).

Adverse event	Fosphenytoin (n = 31)	Levetiracetam (n = 31)	Test statistic	P-value
At 30 minutes				
Sedation	6 (19.4)	3 (9.7)	NA	0.473[a]
Dizziness	1 (3.2)	0 (0.0)	NA	1.000[a]
Fatigue	3 (9.7)	2 (6.5)	NA	1.000[a]
Headache	3 (9.7)	3 (9.7)	NA	1.000[a]
Itching	3 (9.7)	0 (0.0)	NA	0.238[a]
Rash	1 (3.2)	0 (0.0)	NA	1.000[a]
Hypotension	1 (3.2)	0 (0.0)	NA	1.000[a]

Cardiac arrhythmia	1 (3.2)	0 (0.0)	NA	1.000[a]
Respiratory depression	3 (9.7)	2 (6.5)	NA	1.000[a]
At 24 hours				
Sedation	9 (29.0)	1 (3.2)	$\chi^2(1) = 7.63$	0.006
Dizziness	8 (25.8)	4 (12.9)	$\chi^2(1) = 1.65$	0.199
Fatigue	6 (19.4)	4 (12.9)	$\chi^2(1) = 0.48$	0.490
Headache	2 (6.5)	3 (9.7)	NA	1.000[a]
Itching	7 (22.6)	0 (0.0)	NA	0.011[a]
Rash	5 (16.1)	0 (0.0)	NA	0.053[a]
Ataxia	2 (6.5)	0 (0.0)	NA	0.492[a]
Tinnitus	1 (3.2)	0 (0.0)	NA	1.000[a]
Behavioral change	0 (0.0)	1 (3.2)	NA	1.000[a]
At 7 days or discharge				
Sedation	3 (9.7)	2 (6.5)	NA	1.000[a]
Dizziness	3 (9.7)	2 (6.5)	NA	1.000[a]
Fatigue	2 (6.5)	2 (6.5)	NA	1.000[a]
Headache	3 (9.7)	3 (9.7)	NA	1.000[a]
Itching	2 (6.5)	0 (0.0)	NA	0.492[a]
Rash	1 (3.2)	0 (0.0)	NA	1.000[a]
Ataxia	2 (6.5)	0 (0.0)	NA	0.492[a]
Tinnitus	2 (6.5)	0 (0.0)	NA	0.492[a]
Behavioral change	0 (0.0)	1 (3.2)	NA	1.000[a]

TABLE 4: Individual adverse events by treatment group and follow-up time point

Values are presented as n (%). Events that were not observed in either group at a given time point are not listed. No episode of anaphylaxis, Stevens-Johnson syndrome, or purple glove syndrome occurred at any time point. Hypotension, cardiac arrhythmia, and respiratory depression were recorded only at the 30-minute assessment.

[a]Fisher's exact test.

All other p-values are from the Pearson chi-squared test. Test statistics are the Pearson chi-squared value with degrees of freedom (χ^2). NA, not applicable, because Fisher's exact test does not produce a test statistic.

A score of 0 was the most frequent category in both arms (eight and nine patients), death accounted for two and three patients, respectively, and the distribution across the full scale was comparable between the groups (Figure *2*).

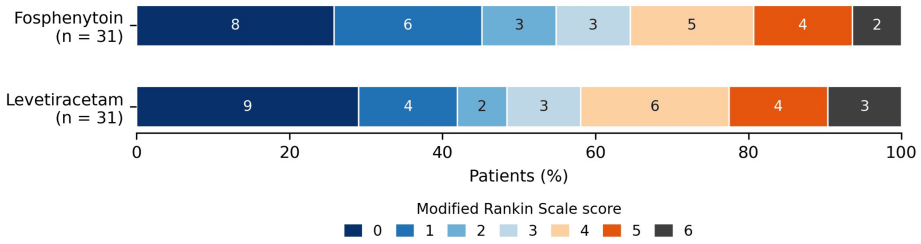


FIGURE 2: Distribution of the modified Rankin Scale score at 7 days or hospital discharge, whichever came first

Numbers within the bars are patient counts.

Discussion

In this trial, levetiracetam and fosphenytoin did not differ significantly in their ability to stop convulsive status epilepticus persisting after diazepam in adults, although the wide CI means that the trial cannot establish equivalence. Among patients who responded, levetiracetam might be associated with faster termination of convulsions and with a longer seizure-free interval before recurrence, whereas fosphenytoin was related to more treatment emergent adverse events at 24 hours, mainly sedation, itching, and rash. Furthermore, levetiracetam was far more often continued as the oral maintenance drug, while intensive care use, intubation, in-hospital mortality, functional outcome at discharge, and drug cost did not differ between the two groups.

This efficacy finding needs careful interpretation. A nonsignificant difference in a trial of 62 patients does not show that two treatments are equivalent. The lower limit of the CI did lie above the noninferiority margin used in the sample size calculation, but a margin of 30 percentage points is wide by clinical standards, the response with fosphenytoin was far lower than the 80% assumed when the trial was planned, and the interval is still compatible with a clinically important advantage for either drug. The result is therefore best read as showing no evidence that levetiracetam is less effective than fosphenytoin in this setting, rather than as proof that the two drugs are interchangeable. The same caution applies to the time to termination and the seizure-free interval, which were compared among responders and among patients with recurrence, respectively, and are therefore not protected by randomization.

Similar to our results, no significant difference in seizure cessation between levetiracetam and fosphenytoin was reported in the Established Status Epilepticus Treatment Trial from the United States and in a multicenter trial from Japan [14,16]. Three meta-analyses that pooled randomized data from adults and children likewise found that neither agent was clearly superior for seizure control [17-19]. An earlier pooled analysis of benzodiazepine-resistant status epilepticus also showed a numerically higher response to levetiracetam than to phenytoin, in the same direction as our finding [28].

In contrast to our study, neither of the two large trials demonstrated a significant safety advantage for levetiracetam, although both recorded numerically more serious adverse events after fosphenytoin [14,16]. The Japanese trial also achieved seizure cessation in more than four-fifths of each group, a considerably higher response than in our cohort. The differences between our results and these trials may be explained by discrepancies in population characteristics, the time from seizure onset to treatment, the drug doses, and the methods of adverse event ascertainment. The American trial enrolled children as well as adults and assessed outcomes under blinded conditions [14], the Japanese trial used a lower fixed dose of levetiracetam, and most of our patients reached the hospital after a prolonged period of uncontrolled convulsions. Seizures that continue for a long time become progressively resistant to drug treatment, partly because inhibitory gamma-aminobutyric acid type A (GABA A) receptors are internalized from the synaptic membrane, and this could explain the lower response in both of our groups.

If confirmed in larger trials, the faster control of seizures with levetiracetam might be attributed to its pharmacological properties. Levetiracetam binds synaptic vesicle glycoprotein 2A and modulates presynaptic neurotransmitter release, and a full loading dose can be infused within 10 minutes. Fosphenytoin is a prodrug that has to be converted to phenytoin, and its infusion rate is restricted because phenytoin blocks cardiac sodium channels and may provoke hypotension, bradyarrhythmia, and conduction block [12]. The excess of adverse events after fosphenytoin might be explained by the same pharmacology. Its central depressant effect could account for the sedation, the transient pruritus that often accompanies fosphenytoin infusion has been linked to its phosphate ester component, and aromatic antiseizure drugs such as phenytoin are well-known triggers of cutaneous hypersensitivity.

A further practical advantage of levetiracetam was continuity of therapy. Because its intravenous and oral formulations are interchangeable at the same dose and do not require serum level monitoring, most patients

simply continued the same molecule orally, which avoided a second drug change during the most unstable phase of admission.

The similar drug cost in the two groups is noteworthy, since the belief that levetiracetam is unaffordable is a frequent reason for choosing fosphenytoin in Bangladeshi hospitals. Formal economic modeling has likewise identified levetiracetam as the most cost-effective non-benzodiazepine option for status epilepticus [29].

These observations are particularly relevant for hospitals where continuous cardiac monitoring and intensive care capacity are limited, a setting in which recent reviews and an international expert survey have stressed the need for safe, simple, and affordable treatment pathways [21,22,30].

The main strengths of this trial are its randomized design, the complete follow-up of every randomized patient, and its conduct in a public tertiary hospital of a resource-limited health system, a setting from which randomized evidence on this question has been lacking. This trial has several limitations. It was conducted at a single center and was not masked, so ascertainment of adverse events and of the precise moment of seizure cessation could have been influenced by knowledge of the allocation. In addition, because the second allocation in each pair followed from the preceding lottery draw and no separate concealment method was used, the assignment of about half of the patients could have been anticipated at enrollment, which introduces a risk of selection bias even though the two groups were well balanced at baseline. The sample was powered for a noninferiority comparison of the primary outcome and was too small to detect modest differences in mortality, intubation, or rare cardiovascular events, and the analyses of time to termination and of the seizure-free interval rest on subgroups of fewer than 20 patients. Most importantly, the absence of a statistically significant difference in the primary efficacy endpoint does not establish equivalence. The CI for the difference was wide, the observed response with fosphenytoin was much lower than the 80% assumed in the sample size calculation, which reduced the precision of the trial, and a clinically meaningful difference in either direction cannot be excluded. Secondary and exploratory outcomes were not adjusted for multiple comparisons, so nominally significant findings such as the shorter time to termination and the longer seizure-free interval with levetiracetam should be regarded as hypothesis-generating. Seizure cessation within 30 minutes was registered as a secondary outcome and is presented here as the primary efficacy endpoint, although both components of the registered primary outcome are reported in full. Electroencephalography was not performed routinely, so non-convulsive status epilepticus persisting after clinical cessation may have gone undetected. Follow-up ended at seven days or discharge, and longer-term functional outcome, seizure recurrence, and drug retention were not assessed. Finally, cost was restricted to the acquisition price of the trial drug and did not capture the cost of monitoring, intensive care, or mechanical ventilation.

Conclusions

In this single-center open-label trial, levetiracetam and fosphenytoin showed no statistically significant difference in stopping benzodiazepine refractory convulsive status epilepticus in adults, but the small sample and wide CI mean that equivalence cannot be concluded. Levetiracetam was associated with fewer treatment emergent adverse events at 24 hours, particularly sedation, itching, and rash, and possibly with faster seizure control among responders, and it was more often continued as oral maintenance therapy, whereas mortality, intubation, functional outcome, and drug cost were similar between the two groups. Adequately powered multicenter blinded trials in resource-limited settings are needed to establish the preferred second-line agent for status epilepticus.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Ethical Review Committee of Dhaka Medical College issued approval ERC-DMC/ECC/2023/131. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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