PEDIATRIC EMERGENCY MEDICINE CRITICAL ARTICLE REVIEW (PEMCAR)

QUESTION	In pediatric patients in convulsive status epilepticus unresponsive to first line therapy with 2 doses of a benzodiazepine, is Levetiracetam superior to Phenytoin as a second line anticonvulsant in improving the rate of seizure cessation 5 minutes after the study drug infusion is completed?
TYPE	Therapy
TOPIC	Neurology: Status Epilepticus
DATE	May, 2019
REVIEWER	Michael Mojica, M.D.
CITATION	Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, Francis KL, Sharpe C, Harvey AS, Davidson A, Craig S, Phillips N, George S, Rao A, Cheng N, Zhang M, Kochar A, Brabyn C, Oakley E, Babl FE; PREDICT Research Network. Levetiracetam versus Phenytoin for Second-Line Treatment of Convulsive Status Epilepticus in Children (ConSEPT): An Open-Label, Multicentre, Randomised Trial. Lancet. 2019 Apr 17. pii: S0140-6736(19)30722-6., PubMed ID: 31005386

STUDY DEFINITIONS	
POPULATION	Inclusion: 1. 3 month-6 years 2. Status epilepticus: International League Against Epilepsy definition a. Unresponsive with continued movements (tonic, jerky) > 5 minutes b. ≥ 2 recurrent seizures without a recovery of consciousness between c. ≥ 3 seizures in the past hour with current seizure 3. Unresponsive to 2 doses of a Benzodiazepine Exclusion: 1. Previously enrolled in study 2. On Levetiracetam or Phenytoin at baseline 3. 2nd line AED in past 24 hours (Levetiracetam, Phenytoin, Phenobarbitone Paraldehyde) 4. History of seizures refractory to Phenytoin 5. Allergy to study drugs 6. Status Epilepticus due to major trauma or eclampsia Setting: PREDICT Network (Australia, New Zealand), n = 13 (8 Children's, 5 General Hospitals), 3/2015-11/2017
INTERVENTION	Levetiracetam: 40 mg/kg IV/IO (maximum dose 3 grams) over 5 minutes (100 mg/ml concentration diluted 1:1 in normal saline (minimum 10 milliliters))
CONTROL	Phenytoin: 20 mg/kg IV/IO (maximum dose 1 gram) over 20 minutes (50 mg/ml concentration diluted 1:4 in normal saline (minimum 20 milliliters))
CO-INTERVENTIONS	First line therapy with 2 doses of a Benzodiazepine (Midazolam: 94%) At 5 minutes after completion of the infusion, if seizure activity continued the patient received the alternative study drug. RSI recommended by local protocols if refractory to initial study medication
OUTCOME	Primary Outcome: Seizure cessation 5 minutes after end of study drug infusion completed: 10 minutes after starting Levetiracetam Infusion (5-minute infusion) 25 minutes after starting Phenytoin infusion (20-minute infusion) Video, if available (67%) was reviewed (2 EM, 1 Neuro) blinded to study group

	Subgroup Analyses: Age (≤ 5 years, > 5 years), focal vs generalized, febrile vs afebrile, 1st line Benzodiazepine (Midazolam vs Other). <u>Secondary Outcomes</u>: 1. Seizure cessation at 2 hours after start of infusion without the need for: a. Further seizure management b. RSI or further seizure management with the exception of the 2nd study agent if the first was not successful 2. Need for RSI for seizure management 3. Time to seizure cessation 4. ICU admission 5. Serious adverse events: a. Death b. Serious unexpected airway complication in the first 24 hours c. Cardiovascular instability: Arrest, arrythmias requiring defibrillation d. Other life-threatening events 6. Length of stay: Inpatient, ICU 7. Seizure status: Earlier of 1 mo after discharge or 2 mo after study entry 8. Safety outcomes: Death, manual airway repositioning, oral or nasal airway placement, positive pressure ventilation, tracheal intubation, fluid bolus, cardiac chest compressions, cardiac defibrillation, allergic reaction, extravasation of intravenous or intraosseous infusions, purple glove syndrome, and any other adverse event reported by clinical staff.
DESIGN	Interventional: Randomized Clinical Trial (Superiority hypothesis)

CRITICAL REVIEW FORM FOR A THERAPY ARTICLE

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized by computer in permuted blocks. An independent statistician prepared the allocation sequence. Randomization was stratified by study site and age (≤ 5 years, > 5 years).
Was randomization concealed?	Yes. An independent pharmacist prepared identical, sealed, opaque envelopes. Patients were allocated based on the next numbered envelope for the appropriate age group.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Treatment groups were similar in demographic characteristics, medical history, seizure type, type and route of initial benzodiazepine received as first line therapy and clinical management prior to the administration of the study medication (Table 1).
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Parents, guardians, treating physicians, research nurses and the investigators were <u>not</u> blinded to the study group.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. The primary outcome was assessed at the time of emergency department care. The research nurse obtained additional information during the initial hospitalization and by phone follow at 1 month. Phone follow up was available for 86% (200/233) of the patients and was similar in both groups.

Were patients analyzed in the groups to which they were randomized?	Yes. The primary analysis was an intention to treat analysis. A per protocol analysis was also performed excluding patients undergoing RSI and intubation between randomization and start of the first study medication. A modified intention-to-treat analysis was also performed excluding patients undergoing RSI and intubation between randomization and start of the first study medication and patients with seizure cessation between randomization and the start of the study drug.
Was the trial stopped early?	No. The trial was not stopped early. The sample size determination required 91 patient per study group (total 182) to determine a difference (effect size) of 20%. 233 patients were included in the primary intention-to-treat analysis.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 233
First line AED: Midazolam 94%
Median time before infusion of the 1st study medication: 73 minutes

PRIMARY OUTCOME: SEIZURE CESSATION 5 MINUTES AFTER INFUSION (TABLE 2)

ANALYSIS	PHENYTOIN	LEVETIRACETAM	RISK DIFFERENCE (95% CI)
Intention to Treat	60% (68/114)	50% (60/119)	-9.2 (-21.9, 3.5%)
Modified ITT[1]	55% (53/96)	46% (46/101)	-9.7 (-23.6, 4.2%)
Per Protocol[2]	60% (67/111)	50% (59/117)	-9.9 (-22.8, 2.9%)

RED = Not statistically significant, GREEN = Statistically significant
1. Excluding 5 patients intubated and 31 patients whose seizure stopped before 1st study drug
2. Excluding 5 patients intubated before 1st study drug
Subgroup Analyses: No difference based on age, focal vs generalized seizure, febrile vs afebrile presentation and 1st line Benzodiazepine used (Midazolam vs Other)
Video confirmation: Available 67%, 4.5% (7/235) disagreement, no difference is primary outcome

SECONDARY OUTCOMES: EFFICACY

	PHENYTOIN	LEVETIRACETAM	RISK DIFF (95% CI)
2hrs: Cessation after 1st AED	54% (62/114)	51% (61/119)	-3.1% (-15.9, 9.7%)
2hrs: Cessation after 2nd AED[1]	24% (27/114)	21% (25/119)	-2.7 (-13.4, 8%)
2hrs: Cessation after 1st or 2nd AED	78% (89/114)	72% (86/119)	-5.8 (-16.9, 5.3%)
Start 1st AED → Termination (min)	22 (IQR 9-49m)	17 (IQR 5-30m)	-5.0 (-13.5, 3.5min)

RED = Not statistically significant, GREEN = Statistically significant
1. Proportion responding to 2nd AED: Phenytoin: 64% (27/42). Levetiracetam: 52% (25/48)

Secondary Outcomes: Adverse Events: No statistically significant difference in:
1. Rate of rapid sequence intubation, rate of ICU admission or length of stay in hospital or ICU
2. Serious adverse events within 2 hours of study medication or during admission (Table 4)
3. Follow-up rate of recurrent seizures or status epilepticus, rate of AED use (Table 5)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence intervals for the risk differences for the primary and secondary outcomes are included in the above tables. The confidence intervals are fairly wide.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Likely, yes. The inclusion of 13 centers that are both children's hospitals and general hospitals in Australia and New Zealand likely make the study's results generalizable to those meeting the study's inclusion and exclusion criteria in a variety of settings. The influence of the inclusion of ethnic groups not typical of the U.S. is unclear but there is no reason to believe that this would influence the study's outcomes. Patient on Levetiracetam or Phenytoin at baseline were excluded so they study results are not applicable to them.
Were all patient important outcomes considered?	Yes. The study included a number of efficacy and safety outcomes in the ED, during admission and at follow-up. The sample size is inadequate to assess the likelihood of rare adverse events such as Stevens-Johnson syndrome.
Are the likely treatment benefits worth the potential harm and costs?	Unclear. There were no statistically significant differences between the 2 study groups in any of the study's efficacy or safety outcomes. However, it is unclear, why the authors utilized a superiority hypothesis rather than an equivalence or non-inferiority hypothesis. As the authors state in their introduction, Phenytoin is associated with a number of serious adverse events. Levetiracetam does not need to be superior to Phenytoin in terms of efficacy to provide a safe alternative to Phenytoin.

CLINICAL BOTTOM LINE

BACKGROUND: Status epilepticus is associated with significant morbidity and mortality. The longer the duration, the greater the risk for adverse outcomes. Benzodiazepines are recommended as first line agents but their efficacy is approximately 50%. The most commonly recommended 2nd line agents are Phenytoin and Fosphenytoin. Their use is associated with an efficacy of approximately 50%. In addition, their use is associated with significant adverse events such as hepatotoxicity, pancytopenia, Stevens-Johnson syndrome, hypotension, arrhythmias and extravasation injury. Levetiracetam (Keppra) had been proven efficacious in small case series, can be administered more rapidly (5 minutes vs 20 minutes) and has the potential fo rfever adverse reaction and drug interactions when compared to Phenytoin and Fosphenytoin.

CLINICAL QUESTION: In pediatric patients in convulsive status epilepticus unresponsive to first line therapy with 2 doses of a benzodiazepine, is Levetiracetam superior to Phenytoin as a second line anticonvulsant in improving the rate of seizure cessation 5 minutes after study drug infusion is completed?

DESIGN/VALIDITY: This was a well-designed randomized clinical trial enrolling patient at 13 Children's and general hospitals in Australia and New Zealand (PREDICT Network). Children in status epilepticus who were not responsive to at least two doses of a Benzodiazepine were included. Patients were randomized to receive Phenytoin: 20 mg/kg IV/IO (maximum dose 1 gram) over 20 minutes or Levetiracetam: 40 mg/kg IV/IO (maximum dose 3 grams) over 5 minutes. If seizure cessation did not occur within 5 minutes of the completion of the study infusion, the

alternative study drug was administered. Allocation was concealed. Parents, guardians, treating physicians and research nurses were not blinded to the allocation group.

The primary outcome was seizure cessation 5 minutes after the completion of study drug infusion (10 minutes after starting Levetiracetam Infusion and 25 minutes after starting Phenytoin infusion). A number of both safety and efficacy secondary outcomes were assessed. Treatment groups were similar with regard to demographic characteristics, medical history, seizure type, type and route of initial benzodiazepine received as first line therapy and clinical management prior to the administration of the study medication (Table 1).

PRIMARY RESULTS: In the primary intention to treat analysis, there was not a statistically significant difference between the two study medication in the primary outcome of seizure cessation 5 minutes after the completion of the study medication infusion (Phenytoin: 60% (68/114), Levetiracetam: 50% (60/119), Risk Difference: -9.2, 95% CI (-21.9, 3.5)). This difference is also considered not clinically significant by the authors criteria of a 20% improvement in seizure cessation for Levetiracetam to be considered superior to Phenytoin. The results were similar in the modified intention to treat and the per protocol analysis. There was no difference in the primary outcome in the subgroup analyses based on age, focal vs generalized seizure, febrile vs afebrile seizure and 1st line Benzodiazepine used.

PRIMARY OUTCOME: SEIZURE CESSATION 5 MINUTES AFTER INFUSION (TABLE 2)

ANALYSIS	PHENYTOIN	LEVETIRACETAM	RISK DIFFERENCE (95% CI)
Intention to Treat	60% (68/114)	50% (60/119)	-9.2 (-21.9, 3.5%)
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1. Excluding 5 patients intubated and 31 patients whose seizure stopped before 1st study drug
2. Excluding 5 patients intubated before 1st study drug
Subgroup Analyses: No difference based on age, focal vs generalized seizure, febrile vs afebrile presentation and 1st line Benzodiazepine used (Midazolam vs Other)
Video confirmation: Available 67%, 4.5% (7/155) disagreement, no difference is primary outcome
RED = Not statistically significant, GREEN = Statistically significant

Of the patients who did not respond to the first study medication, an additional 22% responded to the alternative AED ((Phenytoin: 24% (27/114), Levetiracetam: 21% (25/119)). This could potentially half the rapid sequence intubation rate in those that did not respond to the 1st study medication). The cessation rate after responding to the 1st or second AED was approximately 75% ((Phenytoin: 78% (89/114), Levetiracetam: 72% (86/119)).

There was no statistically significant difference between the two study medications in any of the secondary safety outcomes analyzed. The sample size is inadequate to assess the likelihood of rare adverse events such as Steven's Johnson Syndrome.

APPLICABILITY: The inclusion of 13 centers that are both children's hospitals and general hospitals in Australia and New Zealand likely make the study's results generalizable to those meeting the study's inclusion and exclusion criteria in a variety of settings. The influence of the inclusion of ethnic groups not typical of the U.S. is unclear but there is no reason to believe that this would influence the study's outcomes. Patient on Levetiracetam or Phenytoin at baseline were

excluded so they study results are not applicable to them. An average of 73 minutes elapsed prior to the first study medication. This may not be similar to urban population with shorter transport times and may underestimate the efficacy of the study medications as later treatment is associated with poorer efficacy.

AUTHOR'S CONCLUSION: "In conclusion, we found that levetiracetam is not superior to phenytoin for treatment of children with convulsive status epilepticus with continued clinical seizure activity after treatment with benzodiazepines. Although both drugs were associated with considerable failure rates when given by themselves, treatment with one drug and then the other reduced the failure rate by more than 50%, at the expense of only an additional 10 minutes (compared with giving phenytoin alone). Clinicians should therefore consider sequential use of phenytoin and levetiracetam, or levetiracetam and phenytoin, for management of paediatric convulsive status epilepticus before moving on to RSI and intubation."

POTENTIAL IMPACT: In the intention to treat analysis, Levetiracetam (50%) was found not be not superior to Phenytoin (60%) (Risk Difference: -9.2, 95% CI (-21.9, 3.5)). However, it is unclear, why the authors utilized a superiority hypothesis rather than an equivalence or non-inferiority hypothesis. As the authors state in the introduction, Phenytoin is associated with a number of serious adverse events. Levetiracetam does not need to be superior to Phenytoin in terms of efficacy to provide a safe alternative to Phenytoin. The use of Fosphenytoin compared to Phenytoin could possibly reduce adverse events and eliminate Levetiracetam's time of infusion benefit but at increased monetary cost.

Of the patients who did not respond to the first study medication, an additional 22% responded to the alternative AED ((Phenytoin: 24% (27/114), Levetiracetam: 21% (25/119)). The use of both study medication in sequence could potentially half the rapid sequence intubation rate in those that did not respond to the 1st study medication.

It is important to acknowledge that approximately 50% of the patients were still seizing after the first study drug and 25% after the second alternative study drug. This makes it essential to anticipate the need for addition antiepileptic medications and prepare equipment and medications for rapid sequence intubation.

See also

Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, Woolfall K, Roper L, Noblet J, Lee ED, Potter S, Tate P, Iyer A, Evans V, Appleton RE;
Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI) collaborative.
Levetiracetam Versus Phenytoin For Second-Line Treatment Of Paediatric Convulsive Status Epilepticus (EcLiPSE): A Multicentre, Open-Label, Randomised Trial.
Lancet. 2019 Apr 17. pii: S0140-6736(19)30724-X., PubMed ID: 31005385

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