Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial

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Summary

Background **Phenytoin is the current standard of care for second-line treatment of paediatric convulsive status epilepticus after failure of first-line benzodiazepines, but is only effective in 60% of cases and is associated with considerable adverse effects. A newer anticonvulsant, levetiracetam, can be given more quickly, is potentially more efficacious, and has a more tolerable adverse effect profile. We aimed to determine whether phenytoin or levetiracetam is the superior second-line treatment for paediatric convulsive status epilepticus.**

Methods **ConSEPT was an open-label, multicentre, randomised controlled trial conducted in 13 emergency departments in Australia and New Zealand. Children aged between 3 months and 16 years, with convulsive status epilepticus that failed first-line benzodiazepine treatment, were randomly assigned (1:1) using a computer-generated permuted block (block sizes 2 and 4) randomisation sequence, stratified by site and age (≤5 years, >5 years), to receive 20 mg/kg phenytoin (intravenous or intraosseous infusion over 20 min) or 40 mg/kg levetiracetam (intravenous or intraosseous infusion over 5 min). The primary outcome was clinical cessation of seizure activity 5 min after the completion of infusion of the study drug. Analysis was by intention to treat. This trial is registered with the Australian and New Zealand Clinical Trials Registry, number ACTRN12615000129583.**

Findings **Between March 19, 2015, and Nov 29, 2017, 639 children presented to participating emergency departments with convulsive status epilepticus; 127 were missed, and 278 did not meet eligibility criteria. The parents of one child declined to give consent, leaving 233 children (114 assigned to phenytoin and 119 assigned to levetiracetam) in the intention-to-treat population. Clinical cessation of seizure activity 5 min after completion of infusion of study drug occurred in 68 (60%) patients in the phenytoin group and 60 (50%) patients in the levetiracetam group (risk difference –9·2% [95% CI –21·9 to 3·5]; p=0·16). One participant in the phenytoin group died at 27 days because of haemorrhagic encephalitis; this death was not thought to be due to the study drug. There were no other serious adverse events.**

Interpretation **Levetiracetam is not superior to phenytoin for second-line management of paediatric convulsive status epilepticus.**

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Introduction

Convulsive status epilepticus is the most common life-threatening paediatric neurological emergency.[1] Morbidity and mortality are considerable, with 22% of patients requiring rapid sequence induction (RSI) and intensive care unit (ICU) admission,[2] 34% having neurological sequelae, and mortality occurring in 3–5%.[3] Rapid termination of convulsive status epilepticus is the primary goal of management, in order to avoid neurological sequelae and acute life-threatening complications.[1,4–6]

International management guidelines for paediatric convulsive status epilepticus universally recommend first-line treatment with benzodiazepines.[4–6] This practice is supported by high-level evidence from randomised controlled trials (RCTs) and meta-analyses.[5,7] Benzodiazepines alone are effective in terminating convulsive status epilepticus in only around 40–60% of presentations.[7,8] Subsequent to benzodiazepines, international guidelines recommend phenytoin or fosphenytoin (where available) as second-line agents, followed by RSI, intubation, and ICU admission if second-line agents are ineffective.[4–6] Unfortunately, the evidence base for second-line agents currently consists of observational studies and expert opinion only, with a lack of appropriately powered and designed RCTs.[4,5,7,9] The children who require second-line agents for management of convulsive status epilepticus are at the greatest risk of adverse neurological outcomes.[1,3] Phenytoin is effective in terminating convulsive status epilepticus in only 60% of incidences[8] and has an

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Research in context

Evidence before this study

We searched PubMed in December, 2018, using the terms "phenytoin", or "fosphenytoin", "status epilepticus", and "randomised controlled trials" for published randomised controlled trials (RCTs) of phenytoin versus levetiracetam for second-line treatment of convulsive status epilepticus—ie, benzodiazepine-resistant convulsive status epilepticus—in children and adults. We did not use language restrictions. Reference lists of extracted articles were manually searched for other relevant articles. Of the 48 articles identified in the PubMed search we found three relevant trials, with a further relevant trial subsequently included after manual searching. A small (n=50), single-centre RCT, lacking details on randomisation and allocation concealment, compared fosphenytoin (20 mg/kg) with levetiracetam (30 mg/kg) in children aged 3 months to 12 years with benzodiazepine-resistant convulsive status epilepticus. 5 min after a 7-min infusion of study drug the seizure cessation rate was 84% in the fosphenytoin group and 92% in the levetiracetam group. In adults, a small (n=44) RCT compared phenytoin (20 mg/kg) with levetiracetam (20 mg/kg) in benzodiazepine-resistant convulsive status epilepticus. 30 min after initiation of study drug the seizure cessation rate was 68% in the phenytoin group and 59% in the levetiracetam group. Both studies were underpowered and hence not definitive. Two further small RCTs (n=22–50 per treatment group) in adult patients have compared benzodiazepines plus either phenytoin or levetiracetam, with no difference in seizure cessation rates between groups.

Added value of this study

In this large open-label RCT, the Convulsive Status Epilepticus Paediatric Trial (ConSEPT), conducted in 13 emergency departments in Australia and New Zealand, we found no evidence that levetiracetam was superior to phenytoin as a second-line agent for management of paediatric convulsive status epilepticus. Both drugs were effective (as a single infusion) in controlling seizures in 50–60% of cases after failure of benzodiazepines. In more than 70% of cases, seizure control was maintained for 2 h with use of either drug alone or both drugs sequentially. We found no differences between treatment groups in intubation rates, rate and length of intensive care unit admission, hospital length of stay, or safety outcomes.

Implications of all the available evidence

This study provides the first robustly powered randomised comparison of phenytoin with levetiracetam in second-line management of paediatric convulsive status epilepticus. Although both drugs when given by themselves were associated with considerable failure rates, treatment with one drug followed by the other reduced the failure rate by more than 50%, adding only an additional 10 min to treatment time (compared with giving phenytoin alone). On the basis of the results of this study, and of earlier studies, clinicians should consider sequential use of phenytoin and levetiracetam, or levetiracetam and phenytoin, for second-line management of paediatric convulsive status epilepticus before moving on to the next standard of care, intubation.

adverse event profile that includes hepatotoxicity, pancytopenia, Stevens-Johnson syndrome, severe extravasation injuries, hypotension, and cardiac arrhythmias, and has resulted in death due to intravenous loading dose errors.[10–13]

An alternative to phenytoin for second-line management of convulsive status epilepticus is the broad-spectrum anticonvulsant levetiracetam.[7,9] Over the past two decades levetiracetam has been widely used as prophylaxis for seizure disorders.[14,15] Levetiracetam has several potential advantages over phenytoin when used for convulsive status epilepticus: it can be given rapidly by intravenous infusion (5 min for levetiracetam *vs* 20 min for phenytoin), although central nervous system absorption might be slower; it has reduced risk of serious adverse events (hypotension, cardiac arrhythmias, extravasation, or death); it has greater compatibility with common intravenous fluids; and it has limited drug interactions.[16] Small case series report levetiracetam to have 80% efficacy in second-line management of convulsive status epilepticus.[17–22] However, such reports are subject to selection bias, and no high-level comparative evidence with phenytoin exists.[7,9] Therefore, we did an open-label RCT of phenytoin versus levetiracetam for second-line management of convulsive status epilepticus in children presenting to 13 emergency departments in Australia and New Zealand. The primary aim of the trial was to determine whether levetiracetam or phenytoin is the better second-line treatment for emergency management of convulsive status epilepticus in children.

See Online for appendix

Methods

Study design and participants

The Convulsive Status Epilepticus Paediatric Trial (ConSEPT) was an open-label, multicentre trial conducted in 13 emergency departments in Australia and New Zealand (eight tertiary paediatric hospital emergency departments and five general hospital emergency departments; appendix). All 13 emergency departments are members of the Paediatric Research in Emergency Departments International Collaborative (PREDICT) research network.[23] The trial protocol has been published previously.[24]

Children aged 3 months to 16 years attending one of the participating emergency departments were eligible for enrolment if they presented in convulsive status epilepticus and had received two doses of benzodiazepines

(given by parents, paramedics, or hospital staff) according to local protocols (minimum benzodiazepine dosing to fulfil inclusion criteria are shown in the appendix; eg, midazolam ≥0·1 mg/kg per dose). Convulsive status epilepticus was defined as: being unresponsive with continuing abnormality of movement (increased tone or jerking) for longer than 5 min; or two or more recurrent convulsions without recovery of consciousness between convulsions; or three or more convulsions within the preceding hour and a current convulsion. This definition encompasses the recent International League Against Epilepsy definition.[25]

We excluded children who were previously enrolled and randomly assigned in the study, those who were on regular phenytoin or levetiracetam, those who had been administered second-line anticonvulsants (phenytoin, levetiracetam, phenobarbitone, or paraldehyde) in the past 24 h, those who had a management plan stating that they were refractory to phenytoin, those with a known contraindication or allergy to phenytoin or levetiracetam, those who were in convulsive status epilepticus due to an obvious major head injury, and those who were in convulsive status epilepticus due to eclampsia in late pregnancy.

The trial was approved by the institutional ethics committees at each participating site. We obtained delayed, retrospective, written informed consent from parents or guardians for participants to remain in the study at the earliest possible timepoint after emergency stabilisation for convulsive status epilepticus. Delayed, retrospective, consent can be sought in New Zealand if consent before the intervention is impracticable or undesirable, and in Australia if prospective consent is not practicable, there is potential benefit to the patient, risk is low, the research has merit, and there is no reason to suspect that the parents would not give consent.[24] The ethics committee of one site (Princess Margaret Hospital, Perth, WA, Australia) granted a waiver of consent, so written informed consent was not required from parents or guardians of participants at this site.

Randomisation and masking

Patients were randomly assigned (1:1) to receive levetiracetam or phenytoin. A computer-generated permuted block (block sizes 2 and 4) randomisation allocation sequence was prepared by a statistician independent of the trial team. Randomisation was stratified by site and age (≤5 years, >5 years). A central trial pharmacist, independent of the trial team, placed treatment assignments in sequentially numbered, opaque, sealed, and signed envelopes for each site. At the time of randomisation, each child was allocated to the next numbered envelope maintained for the two age groups at each site. The statistician and pharmacist had no further involvement in the trial after sequence generation and allocation. Parents and guardians, treating physicians, research nurses, and the investigators were not masked to treatment assignment.

Procedures

All children who arrived with convulsive status epilepticus were managed in each site's emergency department resuscitation area. After two doses of benzodiazepines children were assessed for trial inclusion and exclusion criteria. If the patient met eligibility criteria, staff opened the allocation envelope.

Participants assigned to phenytoin received 20 mg/kg intravenous or intraosseous phenytoin (DBL Phenytoin, Hameln Pharmaceuticals, Siegfried Hameln GmbH, Hameln, Germany) infusion over 20 min (50 mg/mL phenytoin; maximum 1 g, diluted 1:4 with 0·9% sodium chloride to a minimum volume of 20 mL). Participants assigned to levetiracetam received 40 mg/kg intravenous or intraosseous levetiracetam (Keppra, UCB Pharma, Braine-l'Alleud, Belgium) infusion over 5 min (100 mg/mL levetiracetam; maximum 3 g, diluted 1:1 with 0·9% sodium chloride to a minimum volume of 10 mL). 5 min after the infusion of trial drug was completed, a formal assessment of seizure activity was performed by the most senior treating physician. The participant was examined for: increased tone; jerking movements (including nystagmoid eye movements); and level of consciousness according to the Alert, Voice, Pain, Unresponsive scale. Continued seizure activity was defined as presence of either increased

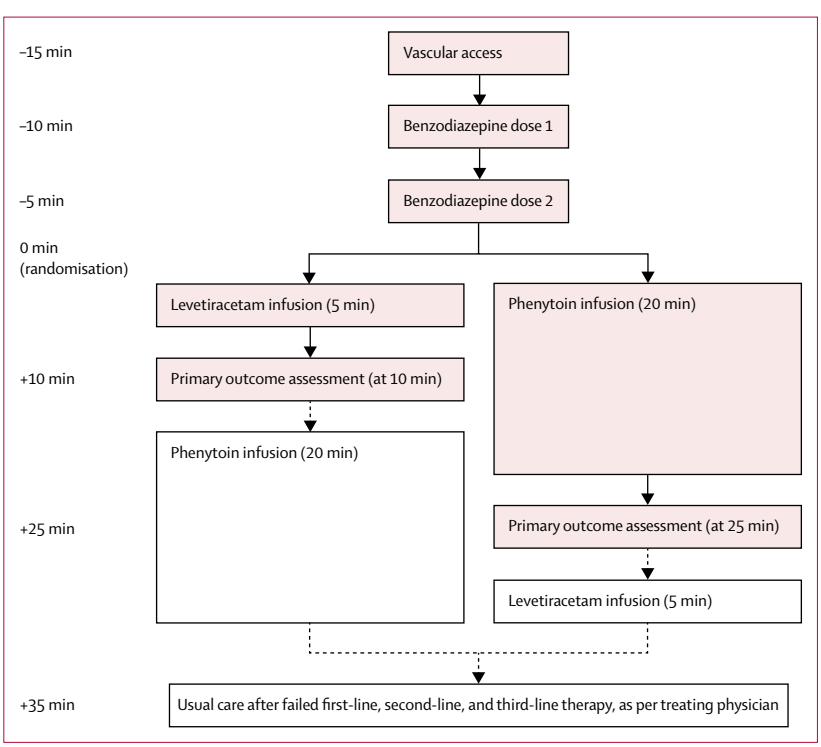

Figure 1: **Study protocol**
Management indicated by dashed lines and white boxes only occurs if convulsive status epilepticus is ongoing at that timepoint.

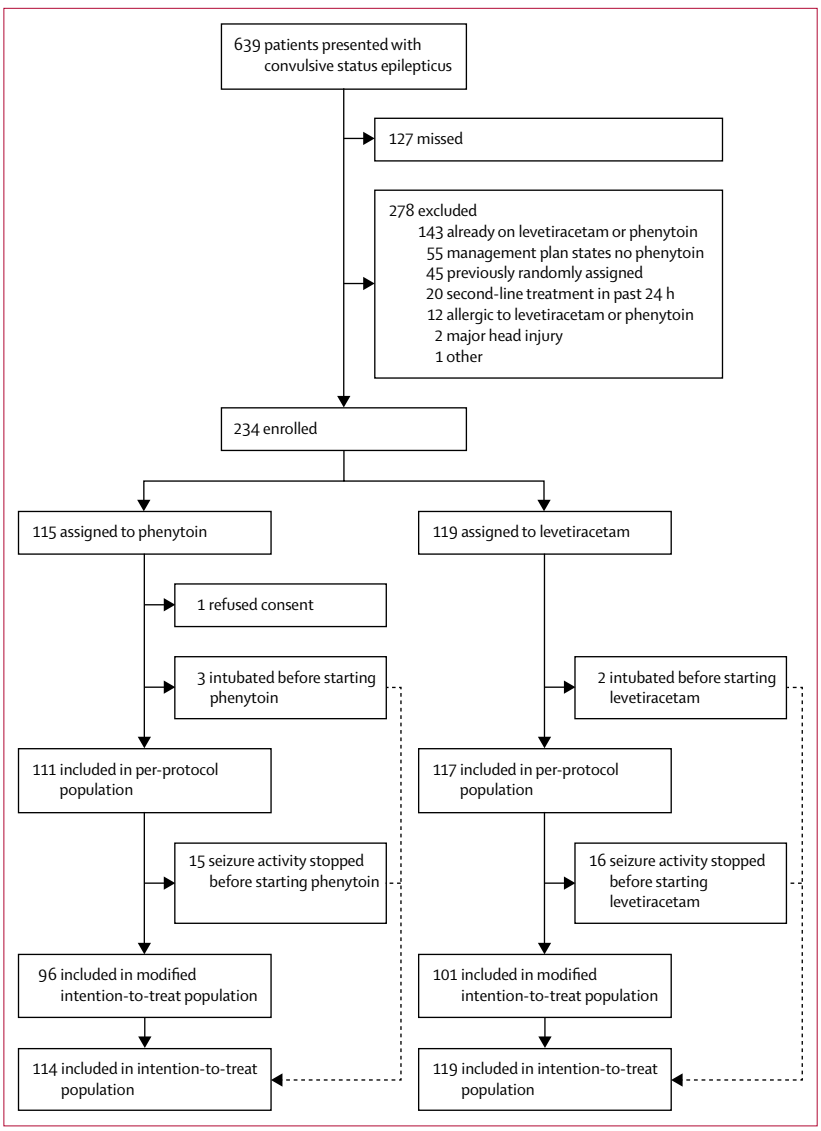

Figure 2: **Trial profile**

tone or jerking movements. If seizure activity was present, the alternative drug was administered, with further assessment of seizure activity performed 5 min after the infusion of the second trial drug was completed (figure 1). If seizure activity was still present participants were managed according to local protocols (all of which advised RSI and intubation). Participants could be managed with any other treatments (including RSI and intubation) as clinically needed, at any time. If clinical cessation of seizure activity (as per above definition) occurred at any stage, the time was recorded and participants finished their current infusion. No further infusions were commenced if participants remained seizure free. If seizure activity recommenced and participants had received only one trial drug, they could receive the alternative trial drug if the clinical treating team felt it to be clinically appropriate.

We recorded: demographics; time of seizure onset; benzodiazepine use; highest temperature; adverse events before trial drugs (airway repositioning, oral or nasal airway placement, application of positive pressure ventilation, tracheal intubation, fluid bolus, chest compressions, and cardiac defibrillation); adverse events in the 2 h after starting trial infusions (in addition to the above: allergic reaction, intravenous or intraosseous access tissue infiltration, extravasation of infusions, purple glove syndrome, and any other significant clinical events as determined by site investigators and clinical treating team).

Trained research nurses visited participants daily while they were inpatients and contacted families 1 month after discharge to collect the following data: past medical history; epilepsy and seizure history; medication history; background of presenting event; family history; length of stay in hospital or ICU; intravenous and nasogastric fluid use; ventilator support; current medications; seizures while in hospital and after discharge; adverse events while in hospital; seizure classification during admission; and neurological investigations.

Outcomes

The primary outcome was clinical cessation of seizure activity 5 min after the completion of infusion of the first trial drug. Because the trial drugs had different optimal infusion rates, this was 10 min after starting levetiracetam and 25 min after starting phenytoin.

If possible, the primary outcome assessment was video-recorded to assess the tone and the presence of jerking limb, face, or eye movements. The intent of the video was to explore possible observer bias due to the unblinded nature of the study design. At study completion, videos were edited by a nurse who was not involved with the study, and all audio or visual clues to treatment allocation were removed. Two emergency physicians and one neurologist, who were masked to treatment allocation, reviewed the videos of assessment of the primary outcome for objective visual or audio evidence that would refute the treating clinician's assessment. Reviewers initially reviewed the videos independently, and then reviewed the videos together, resolving any disagreements by consensus.

Secondary outcomes were clinical cessation of seizure activity 2 h after the commencement of trial infusions without the need for further seizure management after the initial study drug infusion; clinical cessation of seizure activity 2 h after the commencement of trial drug without the need for RSI or further seizure management, apart from receiving the alternative trial drug if first trial drug failed (levetiracetam or levetiracetam plus phenytoin *vs* phenytoin or phenytoin plus levetiracetam); time to clinical seizure cessation; need for RSI for seizure management; ICU admission; serious adverse events, including death, serious unexpected airway complications (endotracheal tube,

laryngeal mask, or cricothyrotomy) in the first 24 h, cardiovascular instability (cardiac arrest or arrhythmia requiring cardiac defibrillation), or other life-threatening events; length of hospital and ICU stay; seizure status 1 month after discharge or 2 months after randomisation (whichever was earliest); and death at 1 month after discharge or 2 months after randomisation.

Safety outcomes were 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.

Statistical analysis

We based the sample size on the hypothesis that levetiracetam would be superior to phenytoin; local retrospective data from 542 cases of convulsive status epilepticus indicated a seizure cessation rate of 60% with phenytoin,[8] and previous retrospective series[17–22] indicated a seizure cessation rate of 80% with levetiracetam. 91 participants were required to be randomly assigned to each group for the study to have at least 80% power to detect an absolute difference in seizure cessation rates of 20% (α=0·05) between groups. To allow for attrition and loss of power due to participants experiencing seizure cessation between randomisation and the start of the first trial drug, 100 participants in active convulsive status epilepticus at the time of starting first trial infusion were recruited per group.

We present summary statistics as number (%) for categorical data and mean (SD) or median (IQR) for continuous data. Analysis of the primary outcome was by intention to treat, with sensitivity analysis undertaken in a per-protocol dataset (excluding participants undergoing RSI and intubation between randomisation and start of the first trial drug) and a modified intention-to-treat dataset (additionally excluding participants experiencing seizure cessation between randomisation and start of the first trial drug). Secondary outcomes and safety outcomes were analysed in the intention-to-treat population. Differences between categorical variables are presented as risk differences (95% CI) and compared using χ^2 tests. Differences between continuous data are presented as differences between means (95% CI; compared using unpaired *t* tests) or medians (95% CI; compared using quantile regression). Prespecified subgroup analyses using logistic regression were proposed based on age (≤5 years *vs* >5 years), focal versus generalised onset of convulsive status epilepticus, febrile versus afebrile convulsive status epilepticus, and type of first-line anticonvulsant used (midazolam *vs* others). However, because logistic regression did not produce evidence of an interaction between treatment group and the subgroups, subgroup analyses were not conducted. An independent data monitoring committee was available to oversee any parental or guardian concerns with the consent process.

De-identified participant data were managed using Research Electronic Data Capture (REDCap), hosted at

	Phenytoin group (n=114)	Levetiracetam group (n=119)
Age		
Mean age, years	4·0 (3·9)	3·8 (3·8)
≤5 years	82 (72%)	85 (71%)
>5 years	32 (28%)	34 (29%)
Sex		
Male	53 (46%)	59 (50%)
Female	61 (54%)	60 (50%)
Race or ethnic group*		
New Zealand or Australian European	55 (48%)	56 (47%)
Aboriginal or Torres Strait Islander	3 (3%)	4 (3%)
Māori or Pacific Islander	16 (14%)	20 (17%)
Other	40 (35%)	39 (33%)
Medical history		
Premature birth†	22 (19%)	21 (18%)
Traumatic brain injury	1 (1%)	3 (3%)
Cerebral palsy	11 (10%)	7 (6%)
Developmental delay	28 (25%)	32 (27%)
Congenital heart disease	6 (5%)	6 (5%)
Previous seizures	55 (48%)	54 (45%)
Previous convulsive status epilepticus	26 (23%)	30 (25%)
Regular anticonvulsant use	22 (19%)	23 (19%)
Family history of seizures	24 (21%)	29 (24%)
History of current status epilepticus presentation		
Febrile	82 (72%)	87 (73%)
Focal onset	14 (12%)	14 (12%)
Median length of seizure before first study drug‡, min	74 (54–99)	72 (50–103)
Midazolam as first-line anticonvulsant	106 (93%)	112 (94%)
Intravenous route	21 (20%)	28 (25%)
Intramuscular route	55 (52%)	53 (47%)
Buccal route	20 (19%)	14 (13%)
Intranasal route	10 (9%)	16 (14%)
Unknown route	0	1 (1%)
Mean midazolam dose as first-line anticonvulsant, mg	2·7 (2·0)	2·5 (1·3)
Clinical management in emergency department before first study drug		
Manual airway repositioning	75 (66%)	87 (73%)
Oral or nasal airway placement	13 (11%)	18 (15%)
Positive pressure ventilation	37 (32%)	40 (34%)
Tracheal intubation	3 (3%)	2 (2%)
Fluid bolus	21 (18%)	28 (24%)
Cardiac compression or defibrillation	0	0

Data are mean (SD), median (IQR), or n (%). *Race or ethnic group was reported by parent or guardian. †Prematurity was defined as birth before 37 weeks of gestation. ‡Time of onset of seizure activity was known in only 102 (89%) participants in the phenytoin group and 101 (85%) participants in the levetiracetam group.

Table 1: **Baseline characteristics**

	Phenytoin group (n=114)	Levetiracetam group (n=119)	Risk difference (95% CI)	p value*
Clinical cessation of seizure activity 5 min after infusion of study drug				
Intention-to-treat population	68 (60%)	60 (50%)	−9·2 (−21·9 to 3·5)	0·16
Modified intention-to-treat population†	53/96 (55%)	46/101 (46%)	−9·7 (−23·6 to 4·2)	0·18
Per-protocol population‡	67/111 (60%)	59/117 (50%)	−9·9 (−22·8 to 2·9)	0·13
Subgroup analysis by age				
≤5 years	49/82 (60%)	43/85 (51%)	..	0·99*
>5 years	19/32 (59%)	17/34 (50%)	..	..
Subgroup analysis by onset				
Focal onset	9/14 (64%)	9/14 (64%)	..	0·21*
Generalised onset	59/100 (59%)	51/105 (49%)	..	..
Subgroup analysis by presentation				
Febrile	45/82 (55%)	44/87 (51%)	..	0·62*
Afebrile	23/32 (72%)	16/32 (50%)	..	..
Subgroup analysis by first-line anticonvulsant				
Midazolam used as first-line anticonvulsant	62/106 (58%)	58/112 (52%)	..	0·15*
Midazolam not used as first-line anticonvulsant	6/8 (75%)	2/7 (29%)	..	..

Data are n (%) or n/N (%), unless otherwise stated. *p value for interaction term in subgroup analyses determined using logistic regression. †Excluding 15 (13%) participants in the phenytoin group and 16 (13%) participants in the levetiracetam group whose seizure activity stopped before the start of the first study drug, and three (3%) participants in the phenytoin group and two (2%) in the levetiracteam group who were intubated before the start of the first study drug. ‡Excluding three (3%) participants in the phenytoin group and two (2%) in the levetiracetam group who were intubated before the start of the first study drug.

Table 2: **Primary outcome and subgroup analyses**

	Phenytoin group (n=114)	Levetiracetam group (n=119)	Difference (95% CI)*	p value
Clinical cessation of seizure activity at 2 h without further seizure management	62 (54%)	61 (51%)	−3·1 (−15·9 to 9·7)	0·63
Received alternative study drug in first 2 h	42 (37%)	48 (40%)	3·5 (−9·0 to 16·0)	0·58
Clinical cessation of seizure activity at 2 h (receiving only one or both study drugs)†	89 (78%)	86 (72%)	−5·8 (−16·9 to 5·3)	0·31
Median time to clinical seizure cessation‡, min	22 (9–49)	17 (5–30)	−5·0 (−13·5 to 3·5)	0·25
Intubation				
Before first study drug	3 (3%)	2 (2%)	−1·0 (−4·7 to 2·8)	0·62
Within first 2 h	13 (11%)	21 (18%)	6·2 (−2·8 to 15·2)	0·18
Subsequently during admission	5 (4%)	8 (7%)	2·3 (−3·5 to 8·2)	0·44
Total	21 (18%)	31 (26%)	7·6 (−3·0 to 18·3)	0·16
Intensive care unit admission	34 (30%)	39 (33%)	2·9 (−9·0 to 14·9)	0·63
Median length of intensive care unit admission§, h	20 (14–29)	33 (22–61)	12·8 (−2·8 to 28·2)	0·11
Median length of hospital admission¶, h	47 (27–76)	52 (37–77)	4·7 (−5·8 to 15·2)	0·38

Data are n (%) or median (IQR), unless otherwise stated. *Data are risk difference (95% CI), or difference between medians (95% CI). †Includes all patients who received phenytoin only, phenytoin plus levetiracetam, levetiracetam only, or levetiracetam plus phenytoin. ‡From commencement of first study drug. Data available for 95 (83%) participants in the phenytoin group and 104 (87%) participants in the levetiracetam group. §Data available for 24 (71%) of 34 participants in the phenytoin group and 25 (64%) of 39 participants in the levetiracetam group. ¶Data available for 114 (100%) participants in the phenytoin group, and 117 (98%) participants in the levetiracetam group.

Table 3: **Secondary outcomes**

The University of Auckland, Auckland, New Zealand, and analysed using Stata, version 15.1.

This trial is registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR), number ACTRN12615000129583.

Role of the funding source

The funders of this trial had no role in trial design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the paper for publication. SRD, KLF, and SD had access to the raw data. The corresponding author had full access to all the data in the trial and had final responsibility for the decision to submit for publication.

Results

Between March 19, 2015, and Nov 29, 2017, 639 children presented to participating emergency departments with convulsive status epilepticus. 127 children were missed, and 278 were excluded, predominantly for being on phenytoin or levetiracetam, having a management plan that stated that phenytoin or levetiracetam was contraindicated, or having been previously enrolled in the study. 234 children were enrolled and randomly assigned: 115 to the phenytoin group and 119 to the levetiracetam group. The parents of one child in the phenytoin group declined to give retrospective consent for use of their child's data, leaving 233 children (114 assigned to phenytoin and 119 assigned to levetiracetam) in the intention-to-treat population (figure 2). 197 patients (96 assigned to phenytoin and 101 assigned to levetiracetam) had active seizure activity at the time of the first study drug. One child assigned to levetiracetam did not receive their assigned study drug because their seizure had terminated; they did not receive any subsequent anticonvulsants.

The two groups were well balanced in terms of baseline characteristics (table 1). Participants had a mean age of 3·9 years (SD 3·8), 112 (48%) were male, 60 (26%) had a history of developmental delay, 109 (47%) had a history of previous seizure activity, and 56 (24%) had a history of previous convulsive status epilepticus. 169 (73%) of convulsive status epilepticus presentations had a febrile trigger, and parents, paramedics, or emergency department staff attempted to terminate the seizure with midazolam in 218 (94%) cases. The median length of seizure activity before infusion of the first study drug was 73 min (IQR 52–99). The median infusion time for the first study drug was 21 min (IQR 20–24) in the phenytoin group and 5 min (5–6) in the levetiracetam group.

The primary outcome, clinical cessation of seizure activity 5 min after the completion of infusion of the first study drug, occurred in 68 (60%) participants in the phenytoin group compared with 60 (50%) participants in the levetiracetam group (risk difference −9·2% [95% CI −21·9 to 3·5]; p=0·16; table 2). Similar results were

	Phenytoin only (n=72)	Phenytoin + levetiracetam (n=42)	Total phenytoin group (n=114)	Levetiracetam only (n=70)	Levetiracetam + phenytoin (n=48)	Total levetiracetam group (n=118)*	Risk difference† (95% CI)	p value
Death, respiratory, and cardiovascular adverse events within 2 h after start of study drug	22 (31%)	20 (48%)	42 (37%)	23 (33%)	32 (67%)	55 (47%)	9·8 (–2·9 to 22·4)	0·13
Death	0	0	0	0	0	0	..	..
Manual airway repositioning	14 (19%)	28 (67%)	42 (37%)	13 (19%)	32 (67%)	45 (38%)	1·3 (–11·2 to 13·8)	0·84
Oral or nasal airway placement	1 (1%)	3 (7%)	4 (4%)	1 (1%)	8 (17%)	9 (8%)	4·1 (–1·7 to 10·0)	0·17
Positive pressure ventilation	7 (10%)	12 (29%)	19 (17%)	10 (14%)	20 (42%)	30 (25%)	8·8 (–1·7 to 19·2)	0·10
Tracheal intubation	8 (11%)	8 (19%)	16 (14%)	7 (10%)	16 (33%)	23 (19%)	5·5 (–4·1 to 15·0)	0·26
Fluid bolus	16 (22%)	17 (40%)	33 (29%)	16 (23%)	25 (52%)	41 (35%)	5·8 (–6·2 to 17·8)	0·34
Cardiac chest compressions	0	0	0	0	0	0	..	..
Cardiac defibrillation	0	0	0	0	0	0	..	..
Other adverse events within 2 h after start of study drug								
Allergic reaction	2 (3%)	2 (5%)	4 (4%)	0	0	0	..	..
Extravasation of intravenous or intraosseous infusions	2 (3%)	1 (2%)	3 (3%)	1 (1%)	0	1 (1%)	..	..
Purple glove syndrome	0	1 (2%)	1 (1%)	0	0	0	..	..
Other	0	2 (5%)	2 (2%)	0	0	0	..	..
Death, respiratory, and cardiovascular adverse events >2 h after start of study drug (during admission)	13 (18%)	13 (31%)	26 (23%)	9 (13%)	15 (31%)	24 (20%)	–2·5 (–13·1 to 7·9)	0·65
Death‡	0	1 (2%)	1 (1%)	0	0	0	..	..
Manual airway repositioning	7 (10%)	8 (19%)	15 (13%)	5 (7%)	8 (17%)	13 (11%)	–2·1 (–10·5 to 6·3)	0·62
Oral or nasal airway placement	1 (1%)	5 (12%)	6 (5%)	2 (3%)	4 (8%)	6 (5%)	–0·2 (–5·9 to 5·5)	0·95
Positive pressure ventilation	5 (7%)	8 (19%)	13 (11%)	6 (9%)	8 (17%)	14 (12%)	0·5 (–7·8 to 8·7)	0·91
Tracheal intubation	0	5 (12%)	5 (4%)	4 (6%)	4 (8%)	8 (7%)	2·4 (–3·5 to 8·3)	0·43
Fluid bolus	8 (11%)	7 (17%)	15 (13%)	2 (3%)	7 (15%)	9 (8%)	–5·5 (–13·4 to 2·3)	0·17
Cardiac chest compressions	0	0	0	0	0	0	..	..
Cardiac defibrillation	0	0	0	0	0	0	..	..
Other adverse events >2 h after start of study drug (during admission)								
Allergic reaction	1 (1%)	2 (5%)	3 (3%)	1 (1%)	2 (4%)	3 (3%)	–0·1 (–4·2 to 4·0)	0·97
Extravasation of intravenous or intraosseous infusions	1 (1%)	3 (7%)	4 (4%)	1 (1%)	1 (2%)	2 (2%)	–1·8 (–5·9 to 2·3)	0·38
Purple glove syndrome	0	0	0	0	0	0	..	..
Other	1 (1%)	1 (2%)	2 (2%)	3 (4%)	3 (6%)	6 (5%)	3·3 (–1·3 to 8·0)	0·16

Data are numbers (%) of participants with an adverse event unless otherwise stated. *One child assigned to levetiracetam did not receive their assigned study drug because their seizure had terminated and is therefore excluded. †Between the total phenytoin group (n=114) and total levetiracetam group (n=118). ‡One participant with haemorrhagic encephalitis died at 27 days after randomisation. Study drug was not thought to have contributed to the death.

Table 4: **Safety outcomes**

obtained in the modified intention-to-treat and per-protocol populations (table 2).

Video recordings were available for 71 (62%) participants in the phenytoin group and 84 (71%) participants in the levetiracetam group (p=0·18). Of the 155 (67%) participants with videos available, clinical cessation of seizure activity 5 min after the completion of the study drug infusion occurred in 45 (63%) participants in the phenytoin group compared with 41 (49%) participants in the levetiracetam group (p=0·26 for interaction term compared with those without video available). On reviewing the videos independent reviewers found evidence to disagree with the clinical team's assessment in almost equal numbers (four for the phenytoin group and three for the levetiracetam group) in both intervention groups of the study (appendix).

There was no evidence for a differential effect of the study drugs in the prespecified subgroups based on age, focal versus generalised onset of convulsive status epilepticus, febrile versus afebrile convulsive status epilepticus, or midazolam used as first-line anticonvulsant versus others (table 2).

At 2 h, 62 (54%) participants in the phenytoin group and 61 (51%) in the levetiracetam group maintained seizure control and did not require further anticonvulsant treatment (risk difference –3·1% [95% CI –15·9 to 9·7]; p=0·63; table 3). 42 (37%) participants in the phenytoin group received levetiracetam for seizure control after

	Phenytoin group (n=100)	Levetiracetam group (n=100)	p value
Regular anticonvulsants	45 (45%)	41 (41%)	0·46
Seizures since discharge	..	..	0·89
Nil	74 (74%)	78 (78%)	..
Daily	5 (5%)	3 (3%)	..
Weekly	4 (4%)	5 (5%)	..
Less than weekly	9 (9%)	9 (9%)	..
Unknown	8 (8%)	5 (5%)	..
Further episode of status epilepticus	9 (9%)	6 (6%)	0·81

14 (12%) patients in the phenytoin group and 19 (16%) patients in the levetiracetam group were lost to follow-up (not able to be contacted).

Table 5: **Follow-up 1 month after discharge, or 2 months after randomisation (whichever was earliest)**

phenytoin, and 48 (40%) participants in the levetiracetam group received phenytoin for seizure control after levetiracetam. Seizure control at 2 h after administration of one or both study drugs was achieved without the need for further anticonvulsant treatment in 89 (78%) participants in the phenytoin group and 86 (72%) participants in the levetiracetam group (risk difference –5·8% [95% CI –16·9 to 5·3]; p=0·31; table 3). 52 (22%) participants underwent RSI of anaesthesia for management of convulsive status epilepticus or airway compromise: five before infusion of study drug, 34 during the first 2 h after commencement of infusion of study drug, and 13 subsequently (21 [18%] intubated in the phenytoin group *vs* 31 [26%] in the levetiracetam group; risk difference 7·6% [95% CI –3·0% to 18·3%]; p=0·16; table 3). Rate and length of ICU admission and hospital length of stay were similar between treatment groups (table 3).

Data on the duration of seizure activity were available for 196 (84%) of the 233 participants. The median time to termination of seizure activity from commencement of first study drug was 22 min (IQR 9–49) in the phenytoin group and 17 min (5–30) in the levetiracetam group (difference –5·0 min [95% CI –13·5 to 3·5]; p=0·25; table 3).

One participant in the phenytoin group died 27 days after randomisation, due to haemorrhagic encephalitis. The death was not thought to be due to study drug by the treating clinical team and investigators. There were no other serious adverse events. Rates of adverse events occurring within 2 h of receiving first study drug, or subsequently during admission, were similar between the two treatment groups (table 4). At hospital discharge, the primary diagnosis was predominantly complex febrile convulsions.

Follow-up data 1 month after hospital discharge were available for 200 (86%) participants. At follow-up, seizure frequency, further episodes of convulsive status epilepticus, and proportion receiving anticonvulsants were similar between treatment groups (table 5).

Discussion

In this open-label, multicentre RCT, we found that levetiracetam was not superior to phenytoin as a second-line agent for management of convulsive status epilepticus in children. Both drugs (given as a single infusion) were effective in controlling seizure activity in 50–60% of cases after failure of at least two doses of benzodiazepines. Further, in more than 70% of cases seizure control could be maintained for 2 h with the use of either drug alone or both drugs sequentially. There was no evidence for differences between treatment groups in any efficacy or safety outcomes.

International management guidelines recommend phenytoin or fosphenytoin as second-line agents for management of convulsive status epilepticus in children after failure of first-line treatment with benzodiazepines.[4–6] These recommendations are currently based on observational evidence, expert opinion, and extrapolation of evidence in adults.[5,7,9] In observational studies, levetiracetam has a reported seizure cessation rate of approximately 80%, although estimates vary widely.[17–22] A small, underpowered (n=50), single-centre trial, lacking details on randomisation and allocation concealment, recently compared levetiracetam (30 mg/kg) with fosphenytoin (20 mg/kg) in children with convulsive status epilepticus aged 3 months to 12 years who did not respond to two doses of benzodiazepines.[26] The authors reported a seizure cessation rate of 84% in the fosphenytoin group and 92% in the levetiracetam group 5 min after a 7-min infusion of study drug.[26] By contrast, our much larger, multicentre RCT found a considerably lower seizure cessation rate with levetiracetam of 50%. Methodological concerns and selection bias in the small RCT and the earlier non-experimental studies are likely to account for the differences in seizure cessation rates between these studies and our study. Of note, our seizure cessation rate with phenytoin (60%) was identical to that found in our previous multicentre retrospective cohort study of convulsive status epilepticus in children (one of the largest reported cohorts to date), suggesting that the sample in our trial is reflective of children with convulsive status epilepticus managed in Australia and New Zealand.[8]

In adult patients, a small, underpowered trial comparing both drugs as second-line treatments for convulsive status epilepticus (n=22 per treatment group) found similar efficacy rates to those in our study, with no difference in primary and secondary outcomes between treatment groups.[27] Two further small trials (n=22–50 per treatment group) in adult patients have compared benzodiazepines plus the addition of either phenytoin or levetiracetam, with no difference in primary or secondary outcomes between groups.[12,28] Paediatric convulsive status epilepticus has a different aetiology and outcome to adult convulsive status epilepticus.[2] However, both drugs reassuringly appear to have efficacy in convulsive status epilepticus of different aetiologies and across a wide age range.

Concern about use of phenytoin in convulsive status epilepticus has focused on its adverse event profile, particularly extravasation, hypotension, and cardiac arrhythmias during infusions.[10–13] In our study, three (3%) patients in the phenytoin group and one (1%) in the levetiracetam group had extravasation of study infusions. All extravasations were promptly identified and no patient required additional interventions, apart from further intravenous access. Numbers of patients requiring intravenous fluid bolus during the first 2 h also did not differ significantly between treatment groups. No patients in either treatment group experienced an arrhythmia requiring intervention. Although our data are reassuring, reports of deaths secondary to arrhythmia during phenytoin infusions exist.[12,13] Potential cardiac toxicity limits the infusion rate of phenytoin (1 mg/kg per min).[13] Further, in 5 years' worth of data from safety incidents related to loading doses reported to the UK National Health Service National Patient Safety Agency, phenytoin was the only drug in which loading dose errors were associated with fatalities.[11] Levetiracetam has a different mechanism of action to phenytoin and has not been associated with deaths during infusions; however, experience with levetiracetam is more limited.[29,30]

Daily use of levetiracetam for seizure prophylaxis has been associated with concerns regarding mood disorders, which only became apparent with increased experience. However, to date, there have been no concerns regarding mood disorders and a single dose of levetiracetam for management of convulsive status epilepticus. This information was not specifically collected in our study.

The primary endpoint used in our study was a pragmatic, real-world endpoint based on international consensus recommendations to terminate seizures as soon as possible, and was consistent with international guidelines, which all recommend further management 5–10 min after any treatment failing to terminate seizure activity.[4–6] Although the definition of seizure cessation used was precise, and required considerable clinical judgment, this endpoint is highly meaningful to clinicians treating a child in active convulsive status epilepticus—ie, it determines whether or not a child requires further treatment. By contrast, trials in adult patients have reported seizure activity 30 min after,[27] and 24 h after, the commencement of study infusion.[12,28] Following failure of a second-line agent (phenytoin or fosphenytoin), international management guidelines for convulsive status epilepticus in children universally recommend control of convulsive status epilepticus with RSI, intubation, and thiopentone or benzodiazepine infusion (or both), with the aim of promptly terminating convulsive status epilepticus.[4–6] However, paediatric emergency RSI and intubation are not without risk and are associated with high use of subsequent health resources, usually requiring ICU admission. Our use of the alternative study drug when the first treatment failed resulted in seizure control without the requirement for further intervention in 27 patients who received phenytoin first (64% of those receiving phenytoin then levetiracetam) and 25 who received levetiracetam first (52% of those receiving levetiracetam then phenytoin). This has important implications for clinical practice; for an additional 10 min of treatment (compared with giving phenytoin alone), the number of children recommended for RSI and intubation can be reduced by more than 50% with little risk of harm.

A novel feature of our study design was the use of video recordings to assess possible observer bias. Videos were available for only 155 (67%) participants; however, there was no evidence of performance bias in terms of treatment allocation or primary outcome assessment. Videos not recorded probably reflected a lack of clinical resources to undertake this secondary activity during emergency management. Of note, the primary outcome in the study was at a fixed point in time when clinicians are required to make a key clinical decision regarding the success of the intervention and to decide whether further treatment is needed. However, the natural history of convulsive status epilepticus is such that seizure activity can return after cessation. This possible return of seizure activity is captured by our secondary endpoints.

Our study has several potential limitations. First, physicians assessing the primary outcome were not masked to the assigned intervention, and therefore there is potential for bias. However, because of the life-threatening nature of convulsive status epilepticus, the senior physician assessing seizure cessation would be unlikely to report that seizure activity had terminated if it had not. Further, in order to reduce this risk, the primary outcome assignment was videoed in 67% of participants. Using these recordings, disagreement between the three independent masked reviewers and the clinical team occurred in almost equal numbers in both intervention groups, suggesting that observer bias did not play an important part. Second, the study was designed as a superiority trial on the basis of published reports of efficacy for both drugs at the time of design, and we attempted to find an absolute difference between treatment groups similar to recent RCT comparisons of first-line benzodiazepines in convulsive status epilepticus.[31] Thus, failure to find a difference does not mean that levetiracetam is statistically equivalent to phenytoin. Third, convulsive status epilepticus and seizure cessation were not confirmed by electroencephalogram. Some pseudo-seizures or seizure mimics could therefore have been included, and some subclinical convulsive status epilepticus or non-convulsive status epilepticus could have occurred when it was thought seizures had terminated. However, this reflects clinical practice and is consistent with similar studies since electroencephalogram is not routinely offered in emergency departments; lack of electroencephalogram is therefore unlikely to have a meaningful impact on our results. Fourth, the timing of primary outcome assessment differed between the two study groups (10 min *vs* 25 min after the start of study

infusions). Although both drugs achieve rapid serum levels following completed infusions, the longer time until primary outcome assessment in the phenytoin group could have allowed for natural seizure decay and effect of benzodiazepines, potentially leading to a bias in favour of phenytoin. However, the effect of levetiracetam would have been biased by using a 20-min infusion time instead of the optimal 5 min. Further, the assessment of the primary outcome 5 min after the completion of the study infusion is consistent with international guidelines. Last, we excluded patients who were taking regular levetiracetam or phenytoin, and those with a management plan stating that they were refractory to phenytoin (no patient had a management plan stating that they were refractory to levetiracetam), and thus the results cannot be extrapolated to these populations.

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 min (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.

Contributors

SRD conceived the study, obtained grant funding, designed the study, provided overall supervision, interpreted the data, and wrote the initial draft of the paper. MLB, JF, MB, JN, AD, SC, NP, SG, AR, NC, MZ, AK, CB, EO, and FEB designed the study, obtained the data, provided supervision, interpreted the data, and revised the manuscript critically. CS and ASH designed the study, interpreted the data, and revised the manuscript critically. SD designed the study, supervised the analysis of the data, interpreted the data, and revised the manuscript critically. KLF analysed the data, interpreted the data, and revised the manuscript critically. All authors gave final approval for the report to be published and agreed to be accountable for all aspects of the work.

Declaration of interests

We declare no competing interests.

Data sharing

We support data sharing. The ConSEPT trial used identifiable individual patient data that are subject to restriction, including ethics, consent, and privacy issues. Anonymised data will be available on request from the corresponding author, where possible within these constraints for use.

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