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Status Epilepticus Australasian Registry for Children (SEARCh): A pilot prospective, observational, cohort study of paediatric status epilepticus.

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Abstract

Objective

Paediatric status epilepticus (SE) has potential for long-term sequelae. Existing data demonstrate delays to aspects of care. The objective of this study was to examine the feasibility of collecting data on children with paediatric SE and describe current management strategies in prehospital and in-hospital settings.

Methods

A pilot, prospective, observational cohort study of children 4 weeks to 16 years of age with SE, in 4 emergency departments in Australia. Clinical details including medications administered, duration of seizure and short-term outcomes were collected. Follow-up occurred by telephone at one month.

Results

We enrolled 167 children with SE. Mean age was 5.4 years (SD=4.1), and 81 (49%) male. Median seizure duration was 10 min (IQR=7 to 30). Midazolam was the first medication administered in 87/100 (87%) instances, mean dose of 0.21 mg/kg (SD=0.13). The dose of midazolam was adequate in 30 (35%), high (>0.2mg/kg) in 44 (51%) and low (<0.1mg/kg) in 13 (15%). For second line agents, levetiracetam was administered on 33/55 (60%) occasions, whereas phenytoin and phenobarbitone were administered on 11/55 (20%) occasions each. Mean dose of levetiracetam was 26.4 mg/kg (SD=13.5). One hundred and four (62%) patients were admitted to hospital, with 13 (8%) admitted to ICU and 7 (4%) intubated.

Conclusion

In children presenting with SE in Australia medical management differed from previous reports, with midazolam as the preferred benzodiazepine, and levetiracetam replacing phenytoin as the preferred second-line agent. This pilot study indicates the feasibility of a paediatric SE registry and its utility to understand and optimise practice.

Introduction/Background

Paediatric status epilepticus (SE) is an important emergency condition, with the potential for significant long-term sequelae. Recent population-based data from New Zealand suggests an incidence of 53 cases per 100,000.(1) Aetiology and outcomes differ from SE in adults, and approximately half of episodes occur in children who are previously well, without prior history of neurodevelopmental problems or epilepsy.(1, 2) SE is frightening for parents and carers, and stressful for health professionals.

In 2015 the International League Against Epilepsy (ILAE) published a classification of SE, which included a time frame of 5 minutes of continuous seizure activity to define SE, rather than 30 minutes.(3) The ILAE also proposed a revised classification of SE with 4 axes; semiology, aetiology, electroencephalographic (EEG) correlates, and age. The semiology or clinical characteristics element of the classification is summarised in table S1. Few studies have utilised this classification system or contemporary definitions, which impacts epidemiological data such as incidence and outcomes.

Age, aetiology, and seizure duration are all associated with outcomes(4), of which only seizure duration is potentially modifiable. Timely treatment, and appropriate escalation of therapy is thought to be vital. Guidelines advocate a stepwise approach with benzodiazepines (usually 2 doses), then a second line agent, followed by rapid sequence induction of anaesthesia to allow further medications to be given without compromising respiratory drive and oxygenation.(4) Existing data demonstrate delays to hospital presentation, anticonvulsant medication administration and treatment escalation are common.(5-7) Recent randomised controlled trial (RCT) data for SE in children have become available (8-10) with guidelines now suggesting the use of a rapid third line agent in order to improve treatment escalation.(11) While these RCTs have increased the quality of the evidence, the studies had considerable exclusion criteria, did not universally include non-convulsive SE or patients experiencing a sudden increase in seizure frequency, which doesn't technically fulfil SE definition. Such children are difficult to include in RCTs due to heterogenicity and pre-existing individualised management plans but do represent a sizable number of patients treated in current SE algorithms.

High quality, prospectively collected, multicentre registry data in paediatric SE can provide vital comparative effectiveness data evaluating current management strategies, complement contemporary clinical trial evidence, assess knowledge translation, generate new research questions and assess feasibility of future clinical trials. The aim of this study was to examine the feasibility of collecting data on a cohort of children presenting with paediatric SE, and to describe current management strategies in prehospital and in-hospital settings, SE aetiology and outcome, and the utility and applicability of ILAE definitions of SE for emergency physicians.

Methods

The Status Epilepticus Australasian Registry for Children (SEARCh) was a pilot, prospective, observational cohort study of children 4 weeks to 16 years of age, in 4 EDs in Australia; two general emergency departments (ED) and two tertiary paediatric EDs. All 4 EDs are members of the Paediatric Research in Emergency Departments International Collaborative (PREDICT) research network.(12)

Children were eligible if they attended a participating ED with SE, defined as seizure activity lasting more than five minutes, recurrent convulsions without recovery of awareness between episodes for more than five minutes, three or more seizures within an hour, or clinically suspected non-convulsive SE.

Patients were prospectively identified by clinical staff at participating EDs. Parents or carers of eligible patients were approached by clinicians or research staff to discuss participation and obtain informed consent. Hospital databases were examined weekly to identify potential missed patients. If a patient left hospital prior to inclusion in the study, an explanatory letter was sent to parents, followed by a telephone call, verbal consent, and enrolment in the study.

Data was recorded on purposely designed case report forms or entered directly into a centralised electronic database. Data relating to ED presentation was recorded by treating clinicians. Research staff recorded details regarding past history, seizure presentation and care during the hospital stay. Follow-up occurred by telephone at one month. Data collected included: Clinical data, interventions, medications administered, complications, duration of seizure, and investigations. This study underwent central ethics review at the Children's Health Queensland Hospital and Health Service (HREC15/15/QRCH/225) and Princess Margaret Hospital (HREC 201611EP) and institutional review at participating hospitals.

Data storage and analysis

De-identified data were managed using Research Electronic Data Capture (REDCap), hosted at Murdoch Children's Research Institute (MCRI), Melbourne, Australia and analysed using Stata (version 16.1 College Station, TX, USA). Descriptive statistics were used for demographic and clinical variables of interest including seizure duration and drug administration, with summary statistics presented as number (%) for categorical data and for continuous data, mean and standard deviation (SD) for normally distributed data and median with interquartile range (IQR) for non-parametric data. To maintain the assumption of independent observations, only the first episode of SE during the study period was included in most analyses. We classified dosing of midazolam as either low, adequate, or high, with adequate defined as between 0.1 and 0.2 mg/kg.

Results

Participants were enrolled from December 2016 to February 2019. The four sites screened and enrolled consecutive patients but had variable enrolment periods based on local resources and research staff availability. In total 1,304 patients were assessed for eligibility, 1,137 were excluded and 167 were consented and enrolled. The vast majority, 942 (83%) of excluded patients did not meet eligibility criteria for SE (usually seizure activity lasting <5 min), 127 (11%) were missed and uncontactable, 23 (2%) caregivers were too distressed to approach, and 14 (1%) caregivers declined participation (Figure 1).

The characteristics of included patients is outlined in Table 1. The mean age was 5.4 years (SD=4.1), and 81 (49%) were male. The median seizure duration was 10 min (IQR=7.0 to 30.0). A prior diagnosis of epilepsy or seizures was present in 119 (71%). 149 (89%) of enrolled patients arrived by ambulance, with a median (IQR) ambulance response time of 10 min (IQR=7 to 14). Classification of seizures at hospital discharge was reported for all bar one participant (Table 2). One hundred (60%) were classified as convulsive SE, 49 (30%) classified as other seizure types with prominent motor signs/symptoms, and 17 (10%) presented without prominent motor symptoms.

One hundred (60%) of participants received an anti-epileptic drug (AED). Of these, the first AED was administered to the child by parents/caregivers (31/100 (31%)), by ambulance personnel (39/100 (39%)) and ED staff (30/100 (30%)) (Table 3). The median time from seizure onset to first AED administered was 24 minutes (IQR=10 to 53). There was no difference in time to administration of

first AED in patients with or without a history of seizures (Table 4). Midazolam was the first AED administered in 87/100 (87%) instances, levetiracetam in 6 (6%), and Clonazepam in 2 (2%) and Diazepam 1 (1%). Lorazepam was not used as a first line AED. Twenty-two (22%) patients received a third dose of benzodiazepine (all midazolam; 7 prehospital, 15 in the ED). The mean first dose of midazolam administered was 0.21 mg/kg (SD=0.13), with little difference between prehospital and ED settings. Of the 87 children who received midazolam as a first-line AED 30 (35%) received an adequate dose, 44 (51%) high dose, and 13 (15%) low dose. Of the 43 children who received further midazolam 26 (61%) received an adequate dose, 8 (19%) high dose, and 9 (21%) low dose.

In terms of second-line AEDs, levetiracetam was administered in 33/55 (60%) whereas phenytoin and phenobarbitone on 11/55 (20%) each. The mean dose of levetiracetam was 26.4 mg/kg (SD=13.5), phenytoin was 18.5 mg/kg (SD=4.9), and phenobarbitone was 8.4 mg/kg (SD=5.4).

One hundred and four (62%) patients were admitted to hospital, with 13 (8%) admitted to ICU, and 7 (4%) intubated. The median length of stay was 17.0 hours (IQR 4.1 to 34.6). Twenty (12%) patients had representations to ED with seizures within a month, most a single visit, some on more than one occasion (Table 2).

Discussion

We present results of a pilot, prospective observational cohort of children with SE presenting to Australian EDs. This represents the largest prospectively collected data on paediatric SE in our region, used new definitions and classifications,(3) and offers important insights into contemporary management of this condition.

Midazolam was clearly the favoured benzodiazepine. This contrasts with other regions like the US where lorazepam is preferred, and rectal diazepam still commonly used.(13) Previous Australasian data suggested diazepam was frequently used per rectum (PR) in the pre-hospital setting and intravenously (IV) in the ED.(5) Our data demonstrates this practice has changed. Midazolam offers advantages as intranasal (IN) or buccal route of delivery is effective for non-medically trained individuals, and the IM route is rapid and easy for ambulance personnel. Administration of PR diazepam is advocated in guidelines but can be difficult and less acceptable in some circumstances.(14) Buccal midazolam also appears to be more efficacious than PR diazepam (4 trials, 648 participants).(15) Ease and familiarity make midazolam a good choice in most scenarios and explains the observed trend in use in Australia.

Delays to benzodiazepine administration are associated with prolonged and refractory seizures and worse outcomes.(16) In our cohort 70% of patients received an AED prior to arrival in ED which compares favourably with 48% previously reported.(5) International studies have reported inadequate initial dosing of benzodiazepines in more than 75% of patients.(13) This was less common in our cohort, with only 15% receiving doses below our recommended range.

Complications may occur with high doses or more than 2 doses of benzodiazepines, the most concerningly being respiratory depression. Of first doses, 51% were classified as high, and a third dose of benzodiazepine was administered in 22% when perhaps escalation to a different class of AED may have been preferable. However, it must be noted that precise dose ranges are not supported by RCT data, but rather based on pharmacokinetic and pharmacodynamic data, expert opinion and consensus. Advanced Paediatric Life Support (APLS) algorithms recommend midazolam 0.15 mg/kg IV, intraosseous (IO), or IM. International guidelines suggest midazolam 10 mg IM if >40 kg, and 5 mg if 13-40kg,(9, 17) which simplifies management, but may lead to wide

variation in weight-based dosages. A recent review found wide dosing variation in prehospital services in Australia and New Zealand.(18) The heterogeneity of midazolam dosing and other AEDs could be useful to explore in high quality, adequately powered, prospectively collected observational data, and could provide evidence regarding the effectiveness of various dosages of midazolam for seizure cessation.

Until recently, there was no high-quality evidence on second line AEDs for children with SE. Guidelines generally recommend phenytoin, but its side effect profile and time required to safely administer the agent are of concern. Recently the ConSEPT, EcLiPSE and ESETT RCTs examined various second line agents in children with benzodiazepine refractory SE and all demonstrated similar efficacy of phenytoin (or fos-phenytoin), levetiracetam and valproate.(8-10) Levetiracetam was the most frequently used second-line agent in our cohort, despite results of these trials not yet being available, and contrasted with previous Australasian data where phenytoin was used 87% of the time.(5) Sites involved in our study participated in the ConSEPT study, so were aware of the emerging role of levetiracetam, and familiar with its ease of use, which may have influenced the early adoption. The optimal dose of levetiracetam is not known with certainty, with doses between 20 and 60mg/kg variably recommended. The dose used in ConSEPT and EcLiPSE was 40mg/kg whereas the dose in the ESETT trial was 60mg/kg. The mean dose observed in our cohort was lower than that used in the RCTs at 26mg/kg. Hospital, national and specialty guidelines should emphasize the dose based on the RCTs and implementation support may be required to ensure that new evidence is incorporated into practice. Phenobarbitone was used as a second-line agent as often as phenytoin. Phenobarbitone has been used for many years, without high level evidence, but it was recently demonstrated to be superior to phenytoin in a randomised trial in a resource poor setting.(19) Although the generalisability to high resource countries needs consideration, it is certainly worthy of further exploration.

International studies have demonstrated delays to second-line agents of more than 60 minutes after seizure onset.(7, 20) Retrospective Australasian data suggest a median time of 24 minutes after ED presentation to the administration of second-line agents,(5) and data from the ConSEPT trial indicated times from seizure onset to second-line medication administration of more than 70 minutes.(8) Our data confirms this is an area that requires attention. Intermittent seizures have been implicated as a risk factor for delays to treatment.(7)

Our study had several strengths including the advantages of prospectively collected data to more accurately record information on time intervals, and classification. We conducted the study in both mixed and tertiary paediatric EDs, and in urban and regional centres in two different states increasing the generalisability of the data. Our study had several limitations. When the accuracy of seizure duration relied on parental report, we used the time of ambulance call as the time of seizure onset due to the common observation of parental overestimation of seizures, which may have resulted in some underreporting of duration. Weight recorded may have included measured and estimates, which may have influenced dosing calculations. There was some missing data, predominantly due to missing ambulance reports required for timing and dosing of medications, and clinical features. Classification of seizure semiology or clinical characteristics was made by the treating clinician, with verification with the discharge diagnosis of the treating team or neurologist without a true gold standard. EEG correlation with seizures was not possible. While of interest, particularly for non-convulsive SE, EEG technology is not currently readily available within Australian EDs. Pseudo seizures and other seizure like events are thought to have been unlikely in the current cohort and the impact on the data in this cohort would have been minimal.

Conclusion

We report the results of a large cohort of children presenting to 4 EDs with SE in Australia. Most children had a previous seizure disorder and received AEDs prior to ambulance or hospital arrival at a higher rate than reported in the past. Medical management in our cohort differs from previous reports with current near universal use of midazolam as the preferred benzodiazepine, and levetiracetam replacing phenytoin as the preferred second-line agent. The data indicate that levetiracetam doses used are likely low and can be optimised. This pilot study indicates the feasibility of a paediatric SE registry and its utility to understand and optimise practice.

Conflict of Interest

Franz Babl and Stuart Dalziel Editorial Board members of the journal and co-authors of this article. They were excluded from the peer-review process and all editorial decisions related to the acceptance and publication of this article. Peer-review was handled independently by members of the Editorial Board to minimise bias.

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Table 1. Characteristics of included patients

N	167
Age [years]	
M (SD)	5.4 (4.1)
Median (IQR)	4.0 (1.8-8.5)
Male sex (%)	81 (49)
Weight [kilograms]*	
M (SD)	21.2 (13.8)
Median (IQR)	16.9 (12.0-26.0)
Seizure duration [minutes]**	
M (SD)	26.8 (39.5)
Median (IQR)	10.0 (7.0-30.0)
Unwell preceding 24 hours, n (%)	82 (49)
Prior Dx epilepsy/prior seizures, n (%)	119 (71)
Presentations, n (%)	
1	147 (88)
2	15 (9)
3	4 (2)
4	0 (0)
5	1 (1)

M, mean; SD, standard deviation; IQR, interquartile range; Dx, diagnosis.
*N=159, **N=152

Table 2. Seizure classification on discharge

N	166	
Prominent motor signs/symptoms		
Present, n (%) [95%CI]	149 (89.8)	[84.1-93.9]
Convulsive SE	100 (59.6)	[51.8-67.2]
Myoclonic SE	5 (3.0)	[1.0-6.9]
Focal motor SE	33 (20.5)	[14.6-27.4]
Tonic SE	10 (6.0)	[2.9-10.8]
Absent, n (%) [95%CI]	17 (10.2)	[6.1-15.9]
NCSE with coma	3 (1.8)	[0.4-5.2]
NCSE without coma	0 (0.0)	[0.0-2.2]
Generalised	8 (4.8)	[2.1-9.3]
Focal (non-motor)	3 (1.8)	[0.4-5.2]
Unknown whether focal or generalised	3 (1.8)	[0.4-5.2]

SE, status epilepticus; NCSE, non-convulsive status epilepticus.

Table 3. Anti-epileptic drug administration

N	100	
First drug administered, n (%) [95%CI]		
Midazolam	87 (87)	[78.8-92.9]
Clonazepam	2 (2)	[0.2-7.0]
Diazepam	1 (1)	[0.0-5.5]
Lorazepam	0 (0)	[0.0-3.6]
Levetiracetam	6 (6)	[2.2-12.6]
First drug route, n (%) [95%CI]		
IM	27 (27)	[18.6-36.8]
IV	13 (13)	[7.1-21.2]
PO	9 (9)	[4.2-16.4]
IO	1 (1)	[0.0-5.5]
PR	1 (1)	[0.0-5.5]
IN	24 (24)	[16.0-33.6]
Buccal	21 (21)	[13.5-30.3]
Unknown	3 (3)	[0.6-8.5]
Other	1 (1)	[0.0-5.5]
First drug administered by…, n (%) [95%CI]		
Parent	31 (31)	[22.1-41.0]
Ambulance	39 (39)	[29.4-49.3]
Emergency Department	30 (30)	[21.2-40.0]
Time to drug administration (minutes), median (IQR)		
Onset to drug 1	24 (10-53)	
Drug 1 to drug 2	25 (10-61)	
Drug 2 to drug 3	18 (5-48)	
Midazolam dose*, n (%) [95%CI]		
Adequate	30 (34)	[24.6-45.4]
High	44 (51)	[39.6-61.5]
Low	13 (15)	[8.2-24.2]

*N=87

Table 4. Comparison of times between onset and first, first and second, and second and third drug administration. P-value from Wilcoxon rank-sum test.

	No Seizure History			Seizure History			
Period (minutes)	n	Median	(IQR)	n	Median	(IQR)	p
Onset to 1st drug admin	27	17	(10.0-33.0)	56	27	(9.5-76.5)	0.20
1st to 2nd drug admin	17	11	(10.0-63.0)	38	30	(13.0-60.0)	0.19
2nd to 3rd drug admin	10	12.5	(5.0-20.0)	30	26	(5.0-60.0)	0.40

IQR, interquartile range.

Figure 1. Participant flow diagram

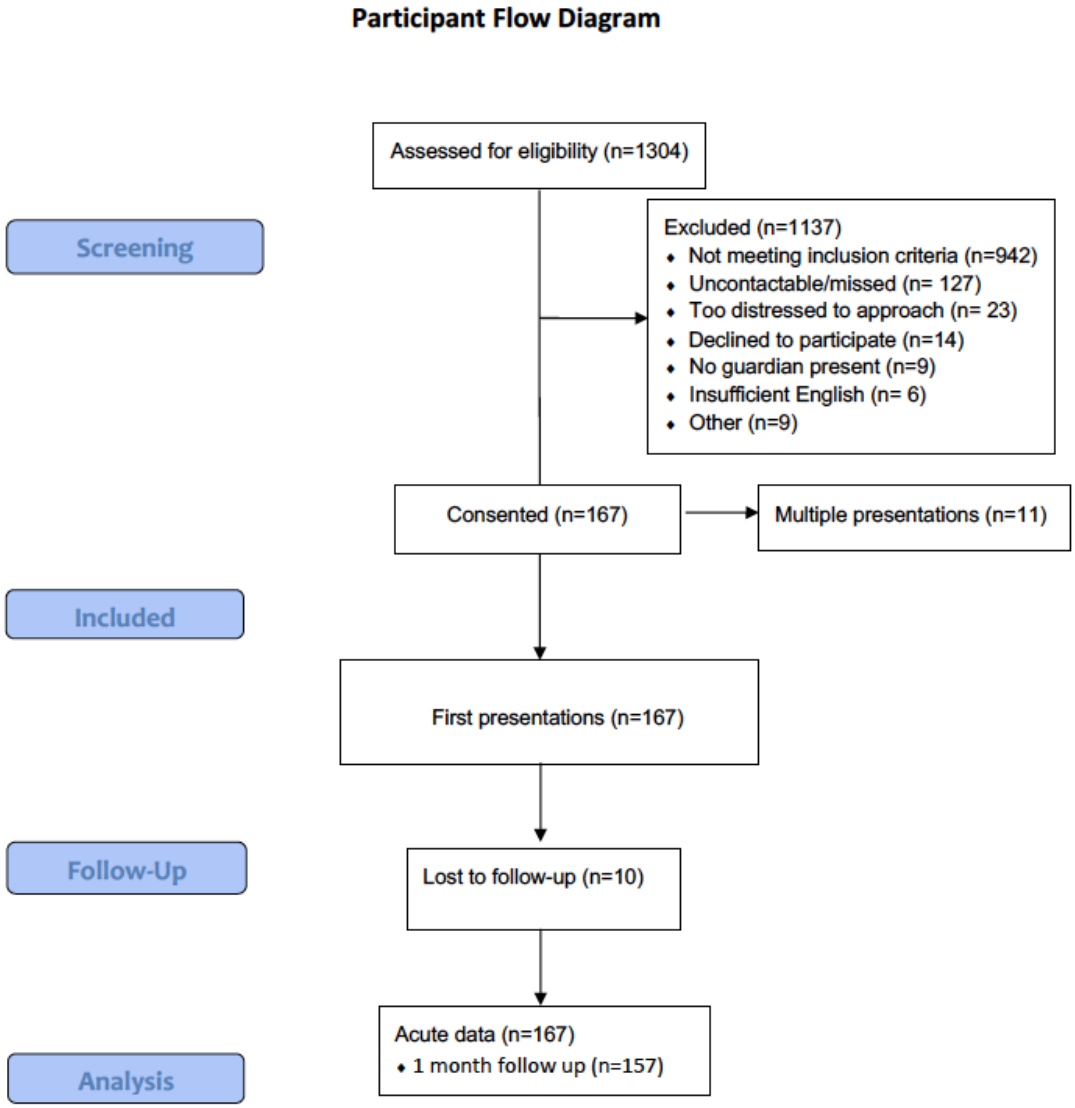

Table S1. Axis 1 Classification of status epilepticus

(A) With prominent motor symptoms

A.1 Convulsive SE (synonym: tonic–clonic SE)
- A.1.a. Generalized convulsive
- A.1.b. Focal onset evolving into bilateral convulsive SE
- A.1.c. Unknown whether focal or generalized

A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
- A.2.a. With coma
- A.2.b. Without coma

A.3 Focal motor
- A.3.a. Repeated focal motor seizures (Jacksonian)
- A.3.b. Epilepsia partialis continua
- A.3.c. Adversive status
- A.3.d. Oculoclonic status
- A.3.e. Ictal paresis (i.e., focal inhibitory SE)

A.4 Tonic status

A.5 Hyperkinetic SE

(B) Without prominent motor symptoms (i.e., non-convulsive SE)

B.1 Non-convulsive SE with coma (including so-called "subtle" SE)

B.2 Non-convulsive SE without coma
- B.2.a. Generalized
- B.2.a.a Typical absence status
- B.2.a.b Atypical absence status
- B.2.a.c Myoclonic absence status
- B.2.b. Focal
- B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/ psychic/experiential, or auditory symptoms)
- B.2.b.b Aphasic status
- B.2.b.c With impaired consciousness
- B.2.c Unknown whether focal or generalized
- B.2.c.a Autonomic SE