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REVIEW ARTICLE

Review article: Paediatric status epilepticus in the pre-hospital setting – an update

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Abstract

Paediatric status epilepticus (SE) is a medical emergency and a common critical condition confronting pre-hospital providers. Management in the pre-hospital environment is challenging but considered extremely important as a potentially modifiable factor on outcome. Recent data from multicentre clinical trials, quality observational studies and consensus documents have influenced management in this area, and is important to both pre-hospital providers and emergency physicians. The objective of this review was to: (i) present an overview of the available evidence relevant to pre-hospital care of paediatric SE; and (ii) assess the current pre-hospital practice guidelines in Australia and New Zealand. The review outlines current definitions and guidelines of SE management, regional variability in pre-hospital protocols within Australasia and aspects of pre-hospital care that could potentially be improved. Contemporary data is required to determine current practice in our setting. It is important that paediatric neurologists, emergency physicians and pre-hospital care providers are all engaged in future endeavours to improve clinical care and knowledge translation efforts for this patient group.

Key words: *ambulance*, *emergency*, *status epilepticus*.

Key findings

- Paediatric status epilepticus is an important condition encountered in the pre-hospital environment, and definitions have evolved.
- Available observational data and pre-hospital protocols suggest there is potential for variability in care.
- Contemporary data are required to determine current practice and optimise care.

Background

Paediatric status epilepticus (SE) is a common medical emergency and is associated with significant morbidity and mortality.[1] SE is one of the most common paediatric life-threatening conditions encountered by pre-hospital providers.[2] In one series, paediatric seizures accounted for one-third of paediatric responses.[3] Many cases present in children with no history of seizures, and can be extremely anxiety provoking for family, bystanders and care providers. Management can be particularly challenging in the pre-hospital environment, and caring for acutely ill children requires a special skill set. Individual front-line pre-hospital providers may have limited experience in these circumstances.

Definitions of SE have evolved over the last few decades, and while historically SE has referred to '30 min' of continuous seizure activity or recurrent seizures without recovery between episodes, more recently an 'operational definition' of SE has been gaining acceptance in guidelines, consensus statements and contemporary clinical trials.[4–6] This operational definition of a seizure lasting more than 5 min is more congruent with treatment guidelines and when one would be expected to commence treatment. The vast majority of seizures cease spontaneously before 5 min, and seizures that continue beyond 5 min are considered unlikely to stop without anticonvulsant medication.[7] Others have termed this 'impending SE' or 'early SE'.[7] Inconsistent definitions make

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interpretation of the existing literature problematic; however, using contemporary definitions of SE as seizures of duration greater than 5 min, and considering ambulance average response times in Australasia, most children who are still seizing when pre-hospital providers arrive at the scene will generally be included in these definitions of SE.

Another difficulty in interpretation of the pre-hospital literature on SE is differences in pre-hospital systems between jurisdictions. Most obvious are the differences in philosophies between the Anglo-American and the Franco-German models of pre-hospital care.[8] In the former, the patient is brought to the doctor, while in the later the doctor is brought to the patient.[8] But even within the Anglo-American system that we have adopted in Australasia, significant differences exist between systems in the UK and USA in terms of training, skills, protocols and response times; therefore, it may be difficult to generalise evidence from one system to others. Even within Australia, generally regarded to have a high level of pre-hospital care, training and protocols vary by state and territory.

While emergency physicians need to be experts on ED management, they also need to understand management issues immediately before arrival in ED and after discharge from ED to ward or home. It is therefore important for ED providers to be aware of current pre-hospital management in their jurisdiction as this may have significant implications on the ongoing management in the ED. Early treatment is thought to be important; therefore, advances in the management of SE targeted the pre-hospital environment.

The objective of the review was to: (i) present an overview of the available evidence relevant to pre-hospital care of paediatric SE; and (ii) assess the current pre-hospital practice guidelines in Australia and New Zealand (NZ). Emphasis will be placed on implications for practice in the Australasian and developed world context, and identify any knowledge gaps and future research priorities in the area.

Methods

A literature search was conducted of Medline (OVID), EMBASE (OVID) and WOS, with the assistance of a medical librarian. The search strategy for Medline is reproduced in Appendix S1. Results of the search were exported to a reference managing database (Endnote X6) and duplicates removed. Titles and abstracts were screened for relevance to pre-hospital SE, and full text of relevant articles were obtained and considered for inclusion. Reference lists of articles identified were screened for additional relevant articles. Database searches were supplemented by grey literature searches using Google scholar. Additionally, pre-hospital service providers in all state and territory jurisdictions were contacted, and protocols for management of SE requested. Results are presented in a narrative form.

Results

Epidemiology

Epidemiological data on SE are limited by inconsistent definitions, variable methodologies and rigour. Studies demonstrate a bimodal age distribution, with peaks in children less than 12 months and adults greater than 60 years.[1] SE is the most common neurological emergency in children with estimated incidence of 20 per 100 000 per year.[1] It is inappropriate to extrapolate evidence from adult studies to children as aetiology and outcomes are vastly different.

Of patients managed in ED, only about one-third of new-onset paediatric SE will occur in children with a history of previous seizures or epilepsy.[1,9] About 10% of first seizures in children with epilepsy present as SE.[10] Aetiology is classified as known or unknown. Known (also called 'symptomatic') causes are further divided into acute or remote.[5] The acute symptomatic causes refer to SE occurring from an acute illness or acute central nervous system insult, for example encephalopathy, meningitis, electrolyte disturbance, hypoxia, trauma, malaria, stroke or intoxication.[1,5,11] SE associated with fever >38.5°C is often called a prolonged febrile seizure (PFS) and occasionally classified as acute symptomatic in aetiology. Outcomes of PFS are generally far better than other causes of acute symptomatic SE. The primary cause is genetic susceptibility to seizure with trigger by fever, rather than SE being caused by the fever itself; therefore, it is more useful to classify PFS as a separate category. Remote symptomatic refers to SE caused by a chronic central nervous system abnormality without an acute provocation.[1,5,11] PFS usually represent about one-third of cases of SE, with acute and remote symptomatic representing about 20% each, and the remainder being 'unknown'.[1,12,13]

Outcomes of SE are better in children than adults. Mortality is estimated at 3–5% overall, higher with refractory cases and significant morbidity in survivors.[1,14] Outcome is dependent on the age of the patient, the cause and the duration of seizure. Although only duration is potentially modifiable, it is not clear whether interventions to reduce the duration of seizure result in improved outcomes. Data supporting the contention that seizure duration per se causes neuronal injury is limited to animal data.[7] From available evidence, the confounding effect of aetiology is inextricably linked to seizure duration and prognosis.[15] Regardless, most algorithms, research efforts and advances in pre-hospital care have been directed at providing effective, timely control of seizure activity, with the expectation that this will lead to improved outcomes.

SE is characterised as convulsive (tonic, clonic or tonic–clonic) or non-convulsive. Non-convulsive SE (NCSE) is a concern of pre-hospital providers and emergency physicians, but the sparse available data is limited to ICU settings,[16] and diagnosis requires EEG, which is often unavailable. Management of suspected NCSE should probably follow algorithms for convulsive SE.

General principles of pre-hospital care

As with any emergency, assessment and management need to occur

simultaneously. Evidence-based guidelines on the pre-hospital management of convulsive SE were published in 2014 and sought to ensure timely seizure cessation, while avoiding respiratory depression and seizure recurrence.[17] Recommendations were invariably based on low- or very-low-quality evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[17] Historically, conducting high-quality clinical trials in SE and paediatric SE has been difficult, but increasingly collaborations and large multicentre trials are occurring including in the pre-hospital setting.[6,18–20]

Any pre-hospital management must take into account the logistical restrictions of this environment, namely lack of space, staff and equipment as well as the necessity for timely transport. Priorities are basic resuscitation requirements of supporting airway, breathing and circulation, timely administration of anticonvulsant medication, identifying likely causes and treating if possible and prevention of secondary consequences of SE.[21] General guidelines on SE management take a stepwise approach;[22,23] typically two doses of benzodiazepine are given first line, if they fail, various second-line anticonvulsants are administered followed by rapid sequence induction of anaesthesia and intubation.[22,23] Pre-hospital providers in the Anglo-American model are usually restricted to benzodiazepines even accepting the common tiered response of most pre-hospital systems. Management beyond first-line agents, including in-hospital settings is based on limited data and expert opinion only. Prompt transport and minimising scene time are important priorities.

Home treatment

Increasingly patients with epilepsy are prescribed management plans that incorporate anticonvulsant administration at home for prolonged seizures, often avoiding ambulance transport.[24] Benzodiazepines are the agent of choice and various routes of administration have been used.[24] Traditionally, rectal diazepam was used because the rectal mucosa provides excellent absorption; however, a number of disadvantages of this route limit utility. Parents or caregivers (teachers, carers and others) may be reluctant to use this route, removing clothes might lead to delays or be inappropriate in public places, physical difficulties of administration while a patient is actively seizing may require multiple individuals or cultural unacceptability in some societies.[25] Other options include intranasal or buccal administration, and midazolam is widely used for this purpose in Australasia. Doses in these settings need to be considered in the subsequent management of children by paramedics and hospital staff, and should not delay escalation to second-line anticonvulsants of a different class. In the field it may be difficult to accurately establish doses and agents administered, but this information is important for continuing care in hospital; ensuring adequate dosing to stop seizures, and avoiding excessive doses with repeated administration with resultant complications. Accurate clinical handover, including events, pre-hospital drugs, timings and doses, is critical information for the decision-making of ED clinicians. Information for management of the acute episode as well as its correct classification is frequently lost in this period.

Which benzodiazepine is best?

The efficacy and safety of pre-hospital treatment of SE by paramedics was first demonstrated in 2001, where both i.v. lorazepam and i.v. diazepam were superior to placebo in a high-quality trial in adults.[26] Although not statistically significant, results hinted at superiority of lorazepam over diazepam, resulting in preferential use where available.[26] Lorazepam is heat labile and requires refrigeration and is not widely available in Australasian settings. The greater efficacy of lorazepam was not supported by a high-quality paediatric trial in 273 children, in which 0.1 mg/kg of i.v. lorazepam was found to have similar seizure termination to 0.2 mg/kg of i.v. diazepam and similar safety profile.[6] A network meta-analysis comparing the efficacy of midazolam, lorazepam and diazepam in treating paediatric SE determined that midazolam had the highest probability of achieving seizure termination.[27]

Pre-hospital guidelines recommended two doses of benzodiazepines and contacting medical control if seizures continue.[17] Subsequent doses of benzodiazepines are discouraged because of the risk of respiratory depression.[28] Observational data suggests up to half of paediatric patients with SE are not receiving any anticonvulsant medication prior to hospital arrival in the USA, UK, Australia and NZ.[1,29,30] Benzodiazepine dosing has also been reported as outside recommended dose ranges in one-quarter of cases.[31] However, methodology of these studies may not identify factors impacting decision-making, for example airway or respiratory concerns or seizures that were intermittent. Prospective and contemporary local data is required to determine if this is an area where practice improvements can be made.

Intravenous access versus other options

Establishing i.v. access in children in the pre-hospital setting is difficult. In children less than 2 years, successful attempts occur only half the time.[32] With active seizures the procedure is even more difficult.[2,33] Although i.v. administration is likely to be preferable if access is already available, administration of medications should not be delayed when immediate i.v. access is not available or difficult. Using non-i.v. routes for the pre-hospital management of paediatric SE is supported by moderate level of evidence.[2,17] Comparable efficacy and side-effect profiles have been demonstrated for sublingual, buccal, intranasal (i.n.), intramuscular (i.m.) and intraosseous (i.o.) routes.[2,34] Per rectum administration is losing favour for issues outlined earlier and the efficacy and ease of use of available alternatives.[5] For non-i.v. routes of administration, the

best efficacy data supports i.n. or i.m. midazolam.[34] Concentrated preparations of midazolam are preferable for i.n. use and may achieve effective concentrations faster than i.m. under ideal circumstances[35] and have the advantage of avoiding needle stick injuries with i.v. or i.m. routes.

The recent landmark multicentre Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) contributed to pre-hospital evidence of adults and children with SE.[20,36] Intramuscular midazolam was superior to i.v. lorazepam for the primary outcome of seizure cessation prior to hospital arrival.[20,36] In the underpowered subgroup of children (n = 120) seizure cessation occurred in 41 of 60 (68.3%) in the i.m. midazolam group, compared to 43 of 60 (71.7%) in the i.v. lorazepam group.[36] Both agents were effective; however, the benefits of shorter time to administration in the i.m. group make this a desirable option for pre-hospital providers in a challenging environment.

Blood glucose

Point-of-care capillary blood glucose testing is recommended in the pre-hospital setting if possible in all children actively seizing[2] and correcting with dextrose or glucagon if below 3 mmol/L.[17] Although this recommendation is based on low-quality evidence and classified as weak, it seems uncontroversial.[17] Although hypoglycaemia is an uncommon cause of SE,[37] it is readily reversible.[11] Glucose testing should not delay the administration of benzodiazepines.[37,38]

Australasian pre-hospital protocols

The various agencies that provide pre-hospital care to children in Australasia provided guidelines for review. Each ambulance service uses midazolam as the pharmacological agent for paediatric seizures.[39–46] Doses and routes of administration are summarised in Table 1. Initial i.v. or i.m. doses are weight based for all services except for Victoria[39] and NZ, which give a bolus dose depending on the child's 'size' or weight range in Victoria,[39] and a bolus dose based on age or parental report of weight in NZ.[40] New South Wales (NSW),[41] Queensland (QLD)[42] and the Northern Territory (NT)[43] protocols allow i.n. midazolam administration at various doses. QLD, South Australia (SA)[44] and the NT protocols also allow midazolam to be delivered through the i.o. route.[42,43] The maximum i.v. single dose varies from 2.5 mg in QLD and NT to 10 mg in Tasmania,[46] and Victoria's protocol varies based on weight.[39] Intramuscular doses are between 1 mg (for an infant) and up to 10 mg in Tasmania.[46] If seizure activity continues, a second dose can be given in each state and territory, although time to second dose ranges between 3 min and 20 min, with 5 min being the median time among the states and territories for i.v. administration. The Australian Capital Territory (ACT) protocol does not specify a time and it states to 'repeat if fitting continues or recurs'.[47] For the states that allow i.n. administration the repeated dose is given after 10 min in QLD,[42] 2 min in the NT[43] and no repeated dose in NSW.[41] Intraosseous doses can be repeated if seizure activities continues for 5 min in both QLD and NT.[42,43]

Protocols in NZ allow for use of a second-line agent if seizure activity continues despite two doses of midazolam. A weight-based regime of approximately 30 mg/kg of i.v. valproate is recommended, administered over 10–15 min (Table 1).[40] Some protocols recommend administration of adjuncts, such as paracetamol in the case of seizures associated with fever.[47]

The differences in these protocols is likely to lead to significant variation in care, although the importance of this degree of variation is uncertain. As is evident from Table 1, the various protocols differ substantially in complexity. Pre-hospital providers need to balance speed and ease of administration in this hostile environment, and the need to reduce complications, which themselves might be more difficult to manage. There is little evidence for the superiority of specific dosing regimes, and artificially precise dosing regimes may not add value when accurate weight estimation in this environment is itself problematic.

ED clinicians need to be aware of local protocols, variability in possible dosing and consider medications delivered in the pre-hospital environment in management decisions in the ED, such as the choice of agent and timing of administration. There is a need for good quality national prospectively collected data on pre-hospital care of patients with SE, to determine how agents are being used, doses given and effectiveness. Evidence-based, consistent and standardised care should be achieved for all children with SE.

Future trends and emerging concepts

Ketamine has received attention in the management of refractory SE.[48,49] While the agent is well known to emergency physicians and increasingly to pre-hospital providers, there is no evidence to suggest the utility in paediatric SE management in this setting at the moment. Large multicentre studies are being conducted in the USA, UK, Australia and NZ, examining the effectiveness of second-line agents levetiracetam and valproate compared to phenytoin.[18,19] Results of these trials are likely to influence recommendations on second-line management in hospitals. There is some interest in the use of second-line agents earlier in the algorithm, including the pre-hospital setting.[50] A pre-hospital study in France addressed this question in adults, and evaluated the effectiveness of adding levetiracetam (a novel second-line agent) to benzodiazepine (clonazepam) in the management of SE in adults.[50] They found no difference in outcomes, but it is likely that if newer second-line agents are shown to be effective, earlier use may be examined.

Conclusion

Paediatric SE represents a significant problem and challenge to pre-hospital care providers. Clinicians

TABLE 1. *Australasian protocols for management of seizures and status epilepticus in children*

	Midazolam first dose†	If seizure activity continues	Second dose
Tasmania	i.m. or i.v.: 0.15 mg/kg (max single dose 10 mg)	i.m.: 10 min i.v.: 5 min	0.15 mg/kg i.v. or i.m. (max single dose 10 mg)
Victoria	i.m. (first line) Infant (5–9 kg) = 1 mg Small child (10–24 kg) = 2.5 mg Large child (>25 kg) = 5 mg	i.m.: 10 min	i.m.: same as original dose
	i.v. (MICA) Infant (5–9 kg) = 0.5 mg Small child (10–24 kg) = 1 mg Large child (>25 kg) = 2 mg	i.v. (MICA): repeat original dose 2–5 min (max 3 doses in addition to i.m.)	i.v.: repeat original dose 2–5 min (max 5 doses)
Australian Capital Territory	i.m.: 0.1 mg/kg	i.m.: 10 min (AP × 1; ICP prn)	i.m.: 0.1 mg/kg
	i.v.: up to 0.1 mg/kg over 2 min i.v. and i.m.	i.v.: 'repeat if fitting continues or recurs'	i.v.: up to 0.1 mg/kg over 2 min i.v.
New South Wales	i.n.: 0.3 mg/kg bolus through MAD, max dose 5 mg	i.n.: no repeat	
	i.m.: 0.15 mg/kg bolus, max dose 5 mg	i.m.: 5 min (max 3 doses total)	i.m.: 0.15 mg/kg bolus, max dose 5 mg
	i.v.: 0.15 mg/kg bolus, max 2.5 mg	i.v.: 3 min (max 3 doses total)	i.v.: 0.15 mg/kg bolus, max dose 2.5 mg
Queensland	i.m. <5 kg = 1 mg 5–10 kg = 2 mg 10–15 kg = 3 mg 15–20 kg = 4 mg >20 kg = 5 mg OR: 0.2 mg/kg	i.m.: 10 min	i.m.: half the initial dose (max 2.5 mg, total max dose 10 mg)
	i.n.: 0.2 mg/kg, single dose max 5 mg, max total dose 10 mg	i.n.: 10 min intervals	i.n.: half the initial dose (max 2.5 mg, total max dose 10 mg)
	CCP only: 0.1 mg/kg i.v. and i.o. single dose max 2.5 mg, max total dose 10 mg	i.v. and i.o.: repeat at 5 min intervals	i.v. and i.o.: 0.1 mg/kg single dose max 2.5 mg, max total dose 10 mg
Northern Territory	i.m.: 0.2 mg/kg, single dose does not exceed 5 mg	i.m.: 10 min intervals	i.m.: repeat at half the initial dose 2.5 mg (no max dose)
	i.n.: 5 mg	i.n.: 2 min PRN	i.n.: 5 mg max dose 10 mg
	i.v./i.o.: 0.1 mg/kg, single dose does not exceed 2.5 mg, no max dose	i.v./i.o.: repeat at 5 min intervals	i.v./i.o.: 0.1 mg/kg, single dose does not exceed 2.5 mg, no max dose
Western Australia	i.m.: 0.2 mg/kg, max bolus 5 mg	i.m.: 10 min	i.m.: 0.2 mg/kg (once)
	i.v./i.o.: 0.1 mg/kg, max bolus 2.5 mg	i.v.: 5 min as needed max of 10 mg	i.v.: 0.1 mg/kg (max 5 mg single bolus)

TABLE 1. *Continued*

	Midazolam first dose†	If seizure activity continues	Second dose
South Australia	i.m.: 0.1 mg/kg, max dose 10 mg	5 min	i.m.: 0.1 mg/kg, max dose 10 mg
	i.v./i.o. (ICP): 0.1 mg/kg, max dose 3 mg	Repeat 'as required'	i.o./i.v.: 0.1 mg/kg, total max dose 0.3 mg/kg
New Zealand	i.v. 5 kg/3 months = 0.5 mg 10 kg/1 year = 1 mg 20 kg/5 years = 2 mg 30 kg/10 years = 3 mg 40 kg/13 years = 4 mg 50 kg/adult = 5 mg	i.v.: 10 min	i.v.: same as the original
	i.m. 5 kg/3 months = 1 mg 10 kg/1 year = 2 mg 20 kg/5 years = 4 mg 30 kg/10 years = 6 mg 40 kg/13 years = 8 mg 50 kg/adult = 10 mg	i.m.: 10 min If seizure activity continues post 2 doses of midazolam: i.v. valproate (over 10–15 min) 5 kg/3 months = 150 mg 10 kg/1 year = 300 mg 20 kg/5 years = 600 mg 30 kg/10 years = 800 mg 40 kg/13 years = 1200 mg 50 kg/adult = 1200 mg	i.m.: same as the original

†All state protocols use midazolam as the drug of choice. AP, advanced paramedic; CCP, critical care paramedic; ICP, intensive care paramedic; i.m., intramuscular; i.n., intranasal; i.o., intraosseous; i.v., intravenous; MAD, mucosal atomising device; MICA, mobile intensive care ambulance.

should be aware of recent changes to definitions of SE. Evidence suggests that the i.m. or i.n. routes are preferable to i.v. in most circumstances in this environment, with highest quality evidence available for i.m. midazolam. There is substantial variation in protocols within pre-hospital services across Australia and NZ. Optimal dosage and timing of administration of subsequent doses are unknown, and future research should address this knowledge gap.

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Competing interests

JF, SD and FEB are section editors for *Emergency Medicine Australasia*.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Appendix S1. Medline search strategy.