

Management of Children with Status Epilepticus

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ABSTRACT

Status epilepticus is defined as generalised convulsions lasting 30 minutes or longer that are continuous or where there is failure to regain consciousness between seizures. The longer the time taken to gain control of seizures, the worse the neurological outcomes for the child, and the harder it is to terminate the seizures. The outcome is further influenced by the underlying aetiology. Treatment of status epilepticus consists of four stages: pre-hospital treatment, emergency department, in-hospital treatment (ward or high care), and anaesthesia (ICU). There are numerous protocols available worldwide. Most are based on the available facilities and the anecdotal preferences of the units involved. Beyond the first level of intervention, there are no large, evidence-based guidelines with which to identify the optimal intervention. Newer agents are increasingly being used, but studies to assess the true efficacy of these are not available. Further, protocols differ between resource-poor countries compared to equipped countries where the capacity to provide intensive care support and expensive medical interventions is limited. There are two targets in the management of status epilepticus, namely the *rapid identification of the underlying aetiology*, as this affects treatment and prognosis, and the *early initiation towards terminating status epilepticus*, which decreases morbidity and mortality.

Keywords: Seizures, Status Epilepticus

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INTRODUCTION

Status epilepticus is defined as generalised convulsions lasting 30 minutes or longer that are continuous or where there is failure to regain consciousness between seizures. This is based on the concept that brain damage through neuronal cell death occurs from this point [1]. Much of this assumption is based on animal experiments, and, in fact, damage can occur with shorter events typically associated with the underlying cause and specific genetic markers, rendering the child more vulnerable [2,3]. Established and refractory status refers to generalised convulsions that last up to and longer than one hour. These seizures are resistant to first, second, and third line interventions, and, as such, require paediatric intensive care intervention. The longer the time taken to gain control of seizures, the worse the neurological outcomes for the child, and the harder it is to terminate the seizures [4]. The outcome is further influenced by the underlying aetiology. For example, a child with encephalitis often suffers the worst neurodisability. There are multifactorial and interlinked issues beyond the seizure duration that affect outcomes. For example, a child under one year of age will suffer from a different infective disease spectrum than older children [5,6,7].

AETIOLOGIES AND DEMOGRAPHICS

The underlying trigger factors for status epilepticus in children are reported to be most commonly due to fever (presumed infection) in 36% of cases, change in medication

(20%), no clear cause (9%), metabolic derangement (8%), congenital malformations (7%), anoxic events (5%), and a diverse array of other factors (trauma, vascular, infection, tumour, drugs) [8,9]. These figures originate from studies of children residing in developed, resource equipped settings and may not be true reflections of the proportions in resource-limited settings, such as South Africa, where neuroinfections are so prevalent.

The mortality in adults is reported at 15-22% and between 3-32% in children. There is no data for South Africa. In a rural population from Kenya, mortality ranged between 15-21%. This was considered an under estimation, with many children suspected to have died before arrival at the hospital [10,11,12,13].

Most children under 5 years of age will typically have generalized tonic clonic seizures (GTCS) that last less than 5 minutes. For younger children and infants, there is a paucity of data, and the suggested timeframe for a typical GTCS is less than 10-15 minutes. The mean age for status epilepticus in children is quoted as 3.4 years in 2 studies [3,9] and less than 1 year in another [14].

INVESTIGATIONS

Optimal investigations for the child in status include blood glucose, anti-epileptic drug (AED) levels (if relevant), toxicology testing and blood cultures, as well as basic biochemistry. Lumbar puncture for cerebrospinal fluid analysis should be considered as clinically indicated and for all children less

than 18 months of age [7]. With a reported yield of only 8%, there is insufficient evidence to recommend routine neuroimaging. Indications supporting neuroimaging would include an unexplained convulsive status, the patient remaining unconscious, or new focal neurological signs becoming apparent [15].

MONITORING

The optimal brain monitoring of the child with suspected sub-clinical seizures should be continuous, non-invasive, highly sensitive to a variety of brain insults, reasonably specific, user friendly, and not too expensive [16]. One such device would be cEEG (continuous EEG – full head montage). This is the optimal tool, but it is not viable in most resource-limited settings. It is effective for identifying non-convulsive seizures and ischaemia. A simpler device is aEEG (amplitude-integrated EEG). This is effective for assessing if burst suppression is attained and for non-convulsive seizures. However, the recording can be affected by potential artefact.

Basic external monitoring (blood pressure, saturation, and heart rate) often underestimates true cerebral function. Cerebral Near-Infrared Spectroscopy (cNIRS) is a non-invasive tool that can be used to assess regional brain saturations (RSO2). Comparison studies with serological markers (S100beta and cNIRS) showed that the latter performed well, better in fact than the S100beta screens [17].

MANAGEMENT

Treatment of status epilepticus consists of four stages: pre-hospital treatment, emergency department, in-hospital treatment (ward or high care), and anaesthesia (ICU).

There are numerous protocols available worldwide. Most are based on the available facilities and the anecdotal preferences of the units involved. Evidence-based data to support these guidelines does not exist. Figure 1 illustrates the protocol followed at the authors centre, Red Cross War Memorial Children's Hospital. This recommendation is also not evidence based but is the most effective regimen to follow for the facilities available to manage these children where intensive care beds are lacking.

First line intervention refers to the care given on arrival at the hospital, regardless of any pre-hospital intervention. Benzodiazepines in the form of diazepam (per rectal, intravenous, or interosseous), midazolam (intranasal, sublingual, intravenous, or interosseous), or lorazepam (per rectal, intravenous, or interosseous) are recommended and can be repeated if necessary. There is acceptance for intervention at this stage with a benzodiazepine and good study data to support it as an intervention [18,19,20]. Comparing diazepam and lorazepam, both are equally effective at aborting status epilepticus. Rectal lorazepam might be more effective than rectal diazepam. Lorazepam has a substantially longer duration of anti-seizure activity; it is lipid-soluble, and, as such, less seizure recurrence is seen and fewer repeat doses are required [21]. Intranasal midazolam is as effective as intravenous diazepam. Buccal midazolam is as effective as rectal diazepam. Intravenous formulations of midazolam (given via buccal or intranasal routes) are relatively inexpensive. Caregivers often prefer to give intranasal midazolam compared to administering rectal diazepam [21].

Paraldehyde is no longer readily available but remains part of some management guidelines [22]. In fact, treatment

with intravenous phenytoin as a second-line therapy was found to be nine times more effective at seizure termination than was treatment with paraldehyde [4].

Second line intervention consists of intravenous phenytoin or phenobarbitone (via intravenous or intramuscular route). Both agents are fairly accepted, but studies are more limited, consisting of small numbers and fewer children [23]. Phenobarbitone can be given as a rapid push and flushed through while monitoring for respiratory depression and hypotension. Phenytoin is administered over 30 minutes through a large vein, but not a central line, using a syringe driver and requires cardiac monitoring for potential cardiac toxicity. It can only be given by intravenous route (in a solution not mixed with dextrose), cannot be repeated, and is not as effective as phenobarbitone [24]. Fosphenytoin would be a more favourable agent. Since it does not contain propylene glycol and has a pH of 8.6-9, it can be administered in dextrose-containing intravenous solutions at a more rapid rate and is equally effective. However, it is three times more expensive than an equivalent dose of phenytoin. Consequently, this agent is not readily available in South Africa and requires Section 21 Medicine Control Council clearance. Experimental rescue therapy with nasogastric phenobarbitone has been used in South Africa. It is given at a dosage of 20mg/kg during second line intervention to patients with good airway protection and the capacity for gastric absorption. This practice was reviewed in a study at Red Cross War Memorial Children's Hospital. Therapeutic levels were attained between 1 to 4 hours after dosage [25]. This practice was found to be safe, there was no need to repeat the dosage to attain therapeutic levels, and for control of seizures, it could be safely repeated. It was considered an effective, viable addition to the protocol, especially where parenteral access or supply of parenteral phenobarbitone was lacking [26,27].

Third line intervention is needed when the child is approaching refractory status. This is a disastrous situation. The child has resistant seizures that are probably exacerbated by the underlying cause, is suffering the secondary complications from the drugs already given, and is developing hypotension and respiratory depression. All these factors adversely affect brain perfusion [5,6,28].

There are no prospective randomised trials comparing the effects of anaesthetics in the treatment of refractory status epilepticus. Safety data is lacking. Existing therapeutic options include barbiturate anaesthetics (Pentobarbital (US) or Thiopental (Europe and Australia), propofol, or midazolam infusions. As regards evidence-based practice, there are no recommendations that can be made on the data available. Even in a large survey of neurologists in United States of America, there was little consensus for third line intervention [29].

Intravenous midazolam infusion requires a syringe driver and carries greater risk of airway suppression, especially following previous benzodiazepine boluses. It takes a long time to gain seizure control, with ranges of 15 minutes to 4.5 hours reported [30,31]. There is the potential for children to be left with prolonged seizures and irreversible neuronal cell death in centres without high care facilities. This intervention is not part of the internationally accepted Advanced Paediatric Life Support (APLS) guidelines [22]. Clonazepam infusions are used in some centres, but there is no evidence to support its use.

Thiopentone is a poor anticonvulsant with marked haemodynamic effects. It has prolonged drug effects if the in-

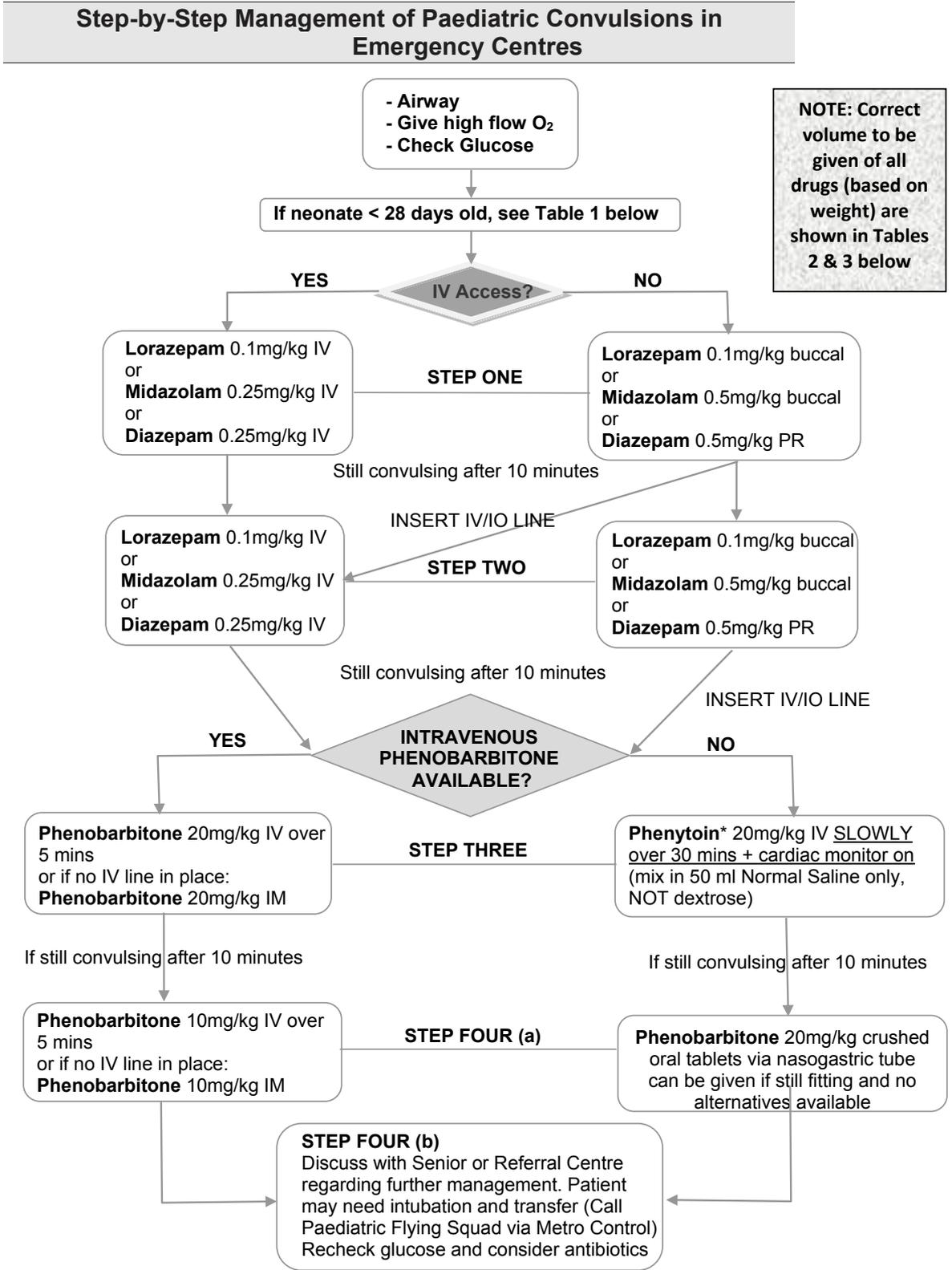


Figure 1

Dose of Phenobarbitone for neonates < 28days. (Note: AVOID BENZODIAZEPINES – High risk of apnoea!)		
Weight of infant	2 kg or less	3 kg
Initial dose of Phenobarbitone, 20 mg/kg, 200 mg/ml solution	0.2 ml	0.3 ml
If convulsions continue after 30 mins, give another dose at 10 mg/kg	0.1 ml	0.15 ml

Acknowledgement: This convulsion protocol is from the Emergency Treatment Assessment & Triage S Africa (ETAT-SA) manual 2011.

fusion is used, and it challenges local ICU capacity where there is limited staffing, monitoring capacity, and anaesthetic experience.

A very high dose of phenobarbitone is reported as a viable option. Both barbiturates and benzodiazepines exert a primary effect on the GABA receptor complex. There is no antiepileptic ceiling effect and no maximum dose. Complications are sedative and have respiratory-depressant properties that are more likely to occur when used in combination with benzodiazepines. Hypotension is unusual, related to the highest phenobarbitone levels, and easily controllable. Such complications are usually related to the underlying aetiology [32].

Intravenous sodium valproate received FDA approval in 1996 for its role in the management of status, but it is not part of the APLS guidelines. There are no reports of respiratory depression or hypotension. It should be used with caution in children with underlying liver disease or suspected mitochondrial disorders, and there is the potential for hepatic encephalopathy to be induced [33]. Valproate performed well in both comparative studies of intravenous sodium valproate versus diazepam infusion and another study of intravenous sodium valproate versus phenytoin. However, there are no large studies measuring efficacy and larger, paediatric focused studies are needed. The agent still requires a syringe driver, and it is expensive. It would be the drug of choice for absence status [34,35].

Intravenous levetiracetam received FDA approval for adults over 16 years in 2006. There is limited data for children (most are retrospective case reviews consisting of n=10 and n=32 children). These children were loaded with 25-50mg/kg as part of third line intervention. The results were effective and safe, but larger comparison studies are needed. The cost of this product currently precludes its availability in many settings [36,37].

Most centres in South Africa follow a policy of repeated parenteral phenobarbitone boluses; this has resulted (anecdotally) in a dramatic reduction in admissions to PICU and the complications of status epilepticus. Parenteral phenobarbitone is listed in the WHO / IMCI guidelines as first line for neonates and second line for infants and children in the management of status epilepticus [40,41]. This agent is

highly effective at controlling status, safe, and inexpensive. If control is not attained within one hour, there should be time to arrange transfer to a tertiary unit; however, in this setting, the need for transfer is exceptional [32,38].

SUMMARY AND FUTURE OPTIONS

There are two targets in the management of status epilepticus

1. *Rapid identification of the underlying aetiology*, as this affects treatment and prognosis.
2. *Early initiation towards terminating status epilepticus*, which decreases morbidity and mortality.

It is possible to recommend benzodiazepines for first line intervention; phenytoin, phenobarbitone, or sodium valproate for second line intervention; and "other medications", such as levetiracetam and pharmacologic coma induction for third line intervention [7]. Future treatments currently under investigation in the adult sector include parenteral lacosamide and oral topiramate loading [1,7]. More extreme interventions include a ketogenic diet, epilepsy surgery, and immunomodulation [20,39]. Although aiming for complete cessation of seizure events is the ideal outcome, it is the underlying aetiology that remains the defining aspect of the outcome for the child.

Competing interests

The author has declared that no competing interest exists.

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