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Is there a need for further trials for the treatment of prolonged seizures?

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ABSTRACT – Prolonged seizures are associated with morbidity and mortality of varying degrees. It is important to recognize seizures early, and treat them appropriately. This leads to the best clinical outcome. There has been an emphasis on prompt treatment, but there exists a variety of poorly executed protocols. This review addresses the question of whether additional clinical trials are necessary, not only to answer for what purpose, but also, clearly, to examine the impact additional studies may have. Overall, the acute treatment of epilepsy emergencies in children has markedly improved with availability of out-of-hospital therapies, but additional studies to determine the most efficacious, maximally safe, and best tolerated treatments are needed.

Key words: status epilepticus, prolonged seizure, acute seizure, treatment, trial, benzodiazepine

Children with seizures experience a spectrum of events extending from isolated, brief seizures to status epilepticus (SE), incorporating a full range of recurrent unprovoked seizures and prolonged or acute repetitive seizures. Similarly, semiology varies from partial to generalised, and non-convulsive to violent and continuing convulsions. This symposium has clearly discussed the early recognition and treatment of repetitive and prolonged seizures because of the deleterious effect with various degrees of morbidity and mortality. Prompt recognition and management leads to the best chance of successful outcome. Further treatment paradigms, appropriate for use in out-of-hospital settings and in hospital, are emphasized and recommended. These protocols must be well designed, and if appropriate, can be followed by the inexperienced and experienced, either caregivers or medical professionals. Even with emphasis on prompt treatment over the past twenty years, there exists a variety of poorly executed protocols. This review addresses the question of whether additional clinical trials are necessary, not only to answer for what purpose, but also, clearly, to examine the impact additional studies may have.

The current definition of SE has shortened from a 30-minute duration of continual recurrent seizures without recovery (ILAE, 1981) to the "operational definition of five minutes or more of continuous seizures or two discrete seizures between

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which there is incomplete recovery of consciousness" (Lowenstein *et al.*, 1999). The latter definition and aggressive early treatment, certainly justified by experimental and clinical data, have demonstrated a tenfold lower rate of mortality for patients with seizures lasting less than 30 minutes. Furthermore, ample data suggests much improved response to first-line therapies if treated earlier. The definition of SE in neonates, however, is even more controversial, as not only timing is argued, SE has so far only been described according to electroclinical, electrographic and clinical features (Morton and Pellock, 2012).

Multiple authors have noted that the outcome of status epilepticus and prolonged or recurrent seizures is dependent upon age, aetiology, and duration of events. Infants younger than one year of age represent a subgroup of children with the highest incidence of SE, whether events, total incidents or recurrences are counted (DeLorenzo *et al.*, 1996; Logroscino *et al.*, 1997). Similarly, causes associated with SE in children are age dependent. Shinnar *et al*. (1997) reported that more than 80% of children younger than 2 years of age had SE resulting from a febrile or acute symptomatic cause. Cryptogenic or remote symptomatic causes are more common in older children. In adults, sub-therapeutic levels of antiepileptic drugs, remote causes, and cerebrovascular disease were the three most common causes of SE (DeLorenzo *et al.*, 1995). Thus, the situation of a child developing SE will differ from neonates to adolescents. For any trial of treatment, appropriate dosing, route of administration, along with time to treatment and definition of repetitive (or clusters of) seizures and SE should be considered. Although it is difficult to correlate treatment with aetiology, large studies may demonstrate differences.

Management and therapy

SE and acute repetitive seizures (clusters) represent neurological medical emergencies. The goals of treatment are noted in *box 1*.

Most prolonged seizures occur out of hospital. Following initial emergent and supportive care, as well as treatment of potential hypoglycaemia, benzodiazepine administration represents the most favoured and evidence-based acute treatment for seizures. Various routes of administration exist, but intravenous is recommended when readily available. Following one or two doses of benzodiazepine, various protocols have been designed and reviewed, with some organizations proposing guidelines, such as the Neurocritical Care Society and American Epilepsy Society. Following benzodiazepine administration, fosphenytoin/phenytoin and valproate are frequently recommended, with some centres continuing the use of phenobarbital. Because of the complexity of studies and clinician bias, there is still argument regarding the best first and second-line therapy. However, most would agree that although a benzodiazepine is the preferred first-line intervention (Rossetti and Lowenstein, 2011). Thus, the primary inquiry may concern which benzodiazepine to use for first-line treatment.

Box 1.
Management Goals for Acute Therapy of Prolonged and Repetitive Seizures

Ensure adequate brain oxygenation and cardiorespiratory function
- Terminate clinical and electrical seizure activity as rapidly as possible
- Prevent seizure recurrence
- Identify precipitating factors, such as hypoglycaemia, electrolyte imbalance, lower drug levels, infection, and fever
- Correct metabolic imbalance
- Prevent systemic complications

Before discussing whether trials could possibly determine which benzodiazepine treatment is superior, a brief review of second-line therapy and trials will be discussed. During the past two decades, protocols were developed in both Europe and the United States which delineated early, established and refractory stages of SE and treatment algorithms. The Veterans Administration study (Treiman *et al.*, 1998) compared combined diazepam and phenytoin, phenytoin alone, phenobarbital, and lorazepam for the treatment of SE and established the more rapid efficacy of benzodiazepine. Subsequently, protocols for refractory SE have been developed and are generally accepted, and have been modified and adopted by different groups (Rosetti and Lowenstein, 2011; Riviello *et al.*, 2013). Second-line preference for phenytoin/fosphenytoin continues, but others have suggested valproate or phenobarbital as nearly equivalent, especially for the treatment of children. Third-line treatment includes midozalam, propofol, and levetiracetam. Pentobarbital, propofol, and anaesthetic agents are typically reserved for refractory or super-refractory cases (Shorvon and Ferlisi, 2011; Rossetti and Lowenstein, 2011). Multi-centre, randomised, double-blind trials were designed to determine the most effective and/or least effective treatments of established status epilepticus in a patient older than the age of 2 years, as opposed to comparing fosphenytoin, levetiracetam, and valproate. The primary outcome measure was cessation of clinical seizure activity and improvement of mental status without serious adverse effects or further intervention at 60 minutes after administration of study drug (Bleck *et al.*, 2013).

Benzodiazepine

Currently in the United States, the only FDA-approved drug recommended for treatment of break-through seizures is rectal diazepam gel. The National Institute of Clinical Excellence (NICE) in the UK recommends rectal diazepam with buccal diazepam for out-of-hospital initial therapy for prolonged seizures in children (NICE, 2012). In other countries, additional preparations are licensed. Furthermore, a number of unlicensed methods for administrating benzodiazepines have been popularized and are currently in use worldwide. Diazepam, alprazolam, clobazam, clonazepam, lorazepam, and midazolam have been used through intravenous, oral, intramuscular, buccal, nasal, and rectal routes. Thus, there is a need for further studies evaluating initial treatment of seizure emergencies. Although there is also a need for paediatric studies of other antiepileptic drugs, this discussion will focus on first-line treatment of paediatric seizures.

Paediatric study variables

Pre-hospital treatment with multiple benzodiazepine preparations has been demonstrated to reduce seizure activity significantly, compared with seizures that remain untreated until the patient reaches the emergency department. The optimal agent for treatment of paediatric seizure emergencies remains unclear, although a recent article concluded that intravenous lorazepam is the expert consensus for first-line treatment of prolonged seizures in children (Riviello *et al.,* 2013). Another suggests that intramuscular midazolam is superior (Silbergleit *et al.,* 2013). Studies that specifically evaluate the paediatric population are limited, and the age range of children recruited varies. Studies have recruited patients as young as 1 month of age (Fişgin *et al.,* 2002) or less than 18 years old, as stipulated as a study criterion (Holsti *et al.,* 2010). The recruitment age of patients in paediatric studies has a larger role than in adult studies because of medication dosing. Children are dosed with benzodiazepines based on weight and age (Diastat^{R}) and if the study does not account for both of these factors, the results are affected.

Location of recruitment will also affect the patient population. For example, studies that are performed in locations such as Sub Saharan Africa will have different aetiologies of prolonged seizures because of the high incidence of cerebral malaria (Malu *et al.,* 2013). The aetiology of the seizures may affect the outcome and response of patients recruited, and makes it difficult to compare studies from different regions. The availability of medications will also be based on the region where the study is performed. For example, intravenous lorazepam is not available in France and clonazepam is used as a first-line benzodiazepine (Hubert *et al.,* 2009), which is not available in the United States.

Inclusion criteria and outcome vary between studies. Seizure emergencies include acute seizure management of repetitive seizures, prolonged seizures, and SE. The inclusion criteria definition can vary for each of these situations and the possibilities are too numerous to enumerate. There are primary outcome and secondary outcome measures that include time to treatment, superiority of route of administration or drug, seizure cessation, and seizure recurrence. The different outcomes make comparison and analysis of multiple studies challenging.

Medication formulation

There are numerous studies that compare the different benzodiazepines as abortive treatment in children, but the formulation of the medications used differs even when similar routes are used. Midazolam is an example of a medication that has been studied as an intranasal medication option, but in some studies the available intravenous formulation was dripped into the nose (Lahat *et al.,* 2000; Mahmoudian and Zadeh, 2004; Bhattacharyya *et al.,* 2006; Javadzadeh *et al.,* 2012; Thakker and Shanbag, 2013), while in others it was sprayed into the nares (Fişgin *et al.,* 2002; Holsti *et al.,* 2010). Buccal midazolam formulations include maleate and the classic intravenous preparation. This can affect the efficacy and adversity of the treatment because different delivery preparations and systems are difficult to compare. Nevertheless, efficacy is reported.

Routes of administration

It is difficult to compare studies when there are different routes of medication administration, especially when two different medications are compared. It is well accepted that the time required to administer an intravenous preparation in a convulsing patient can delay treatment and prolong seizure duration. For example, studies have concluded that seizure cessation was faster with diazepam, but the time to administer intravenous diazepam was greater than that for intranasal midazolam (Lahat *et al.,* 2000; Mahmoudian and Zadeh, 2004; Javadzadeh *et al.,* 2012). Time and ability to establish intravenous access has led some to interosseous administration. The overall treatment effect (time to administer treatment *and* achieve seizure cessation) was significantly improved with intranasal midazolam when compared with intravenous diazepam (Mahmoudian and Zadeh, 2004; Bhattacharyya *et al.,* 2006; Javadzadeh *et al.,* 2012; Thakker and Shanbag, 2013). Comparing rectal, intranasal, and intravenous formulations can cause

confusion because of the factors that affect time to administration.

The RAMPART trial (Rapid Anticonvulsant Medication Prior to Arrival Trial) reported a double-blind randomised clinical trial to determine if the efficacy of intramuscular midazolam is non-inferior by a margin of 10% to that of intravenous lorazepam in patients treated by paramedics for SE (Silbergleit *et al.,* 2013). SE was defined as the patient actively convulsing upon EMS arrival. The study concluded that patients treated with intramuscular midazolam were more likely to have stopped seizing on arrival to the emergency department and were less likely to require any hospitalisation or admission to an intensive care unit. This was a large study, included adults and paediatric patients, and concluded that intramuscular midazolam is not less effective, but not superior. Further review of the results of the study support that "*intramuscular midazolam is the best option for the prehospital treatment of status epilepticus*" (Silbergleit *et al.,* 2013).

A meta-analysis was published in 2010 to evaluate midazolam versus diazepam in children and young adults (McMullan *et al.,* 2010). The study concluded that for seizure cessation, midazolam by any route was superior to diazepam, non-intravenous midazolam was as effective as intravenous diazepam, and buccal midazolam was superior to rectal diazepam with regards to achieving seizure control. The limitation of this meta-analysis is that all studies included were relatively small and were not standardised relative to dose, outcomes, and inclusion criteria. The results support the conclusion that more larger and standardised studies are needed to determine superiority of a benzodiazepine.

Discussion and conclusion

Cross *et al*. (2013) recently published an intriguing paper entitled "*Are we failing to provide adequate rescue medication to children at risk of prolonged convulsive seizures in schools?*" They highlighted current guidelines recommending immediate treatment of children to prevent progression to status epilepticus and emphasized that a more systematic response is needed to ensure that children receive rescue medication regardless of where their seizure occurs. In the United States, local regulations may allow or disallow administration of benzodiazepine. Certain cultures will find it socially difficult to administer the rectal formulation in all but the youngest of children. Furthermore, international agreement and availability of medication differs. In 2009, Hubert reported that intravenous lorazepam was not available in France. Furthermore, buccal midazolam is not licensed in the United States. Their suggestion of using intravenous clonazepam may be appropriate in some countries, but this preparation is not available in the United States.

With this degree of practical concern and controversy, the academic scientist/clinician must certainly request additional studies to answer which agent is the most effective and safe for the management of acute seizures in children. In the UK, Chin reported that only one in every six children with SE admitted to the paediatric intensive care unit was appropriately treated using existing current guidelines. In the United States, the Febrile Status Epilepticus Study (FEBSTAT) demonstrated significant diversity, not only in home therapy for those with recurrent events, but in emergency services for initial treatment of SE. Furthermore, inadequate dosing was administered in a third of patients (Seinfeld *et al*., 2014). Similar disparities are noted across the UK and Europe for the administration of rescue medications in children with prolonged acute convulsive seizures in the community (Wait *et al.,* 2013).

Further trials on treatment of acute seizures are needed

A large study to determine paediatric guidelines or algorithm for the treatment of seizure clusters (ARS) and prolonged seizures should be performed. Although it is accepted that treatment with benzodiazepine is first-line and should not be delayed, there is a lack of data to determine optimal benzodiazepine route, dose, or preparation.

There are fewer studies performed on acute paediatric seizures compared to those in adults. Larger paediatric studies are needed in paediatric seizure emergencies to determine first-line treatment and subsequent treatment. There is mounting evidence that supports multiple safe and effective alternative routes of benzodiazepine administration for rapid treatment of seizure emergencies in children. These studies must carefully define definition for treatments, appropriate dosing, age and aetiology of subjects, clearer outcome criteria (clinical, electrographic, or both), tolerability, and safety. Our belief is that there may be no single agent or method of administration optimal for all patients. Different age groups and personal preference of patients or caregivers will determine the "best" preparation for an individual. Nevertheless, studies will tell us if various compounds are comparable with regards to their efficacy and/or time to effectiveness. Certainly other factors will be important.

So, do we need further studies? YES!

Will this be easy to accomplish? No!

Our advice is to proceed with caution using large consortia with well-defined study criteria and end points. We all strive to provide the best and most efficient

treatment of potential seizure emergencies in children. Perhaps the greatest need for studies is to establish the acceptance of these therapies among those treating children. These investigations require the interaction of social scientists with medical professionals and lay organisations to establish best practices.
Overall, the acute treatment of epilepsy emergencies in children has markedly improved with availability of out-of-hospital therapies. Additional studies to determine the most efficacious, maximally safe, and best tolerated treatments are needed. We must also learn from those receiving and administering these treatments to optimize treatment for children of various ages with differing requirements. Still, we have unmet needs. □

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