The BC Children's Emergency Clinical Practice Guidelines

Management of Convulsive Status Epilepticus in Infants and Children

Created September 2007

Modified 25 August 2008**Key Points:**

1. Convulsive status epilepticus is a medical emergency
2. Early treatment of status epilepticus is more effective in stopping the seizure.
3. Benzodiazepines are the first-line treatment after stabilization of airway, breathing, and circulation.
4. Treatment with phenytoin should be initiated immediately following benzodiazepines.
5. Refractory status epilepticus is defined as status epilepticus unresponsive to a benzodiazepine and phenytoin. It requires adminstration of an anesthetic agent such as midazolam or a barbiturate and transfer to an intensive care setting.
6. Initial investigations and history should focus on metabolic derangements, infections, and other causes that require immediate treatment.

INTRODUCTION AND BACKGROUND

Status epilepticus is defined as continuous seizure activity lasting for 30 minutes or recurrent seizures without any intervening recovery of full consciousness and represents one of the major medical emergencies in children. Status epilepticus can be classified according to seizure type. This guideline deals with convulsive status epilepticus occurring in children and infants outside the neonatal period.

The majority of seizures stop spontaneously within 5 minutes. However, most seizures that last for longer than 7 minutes will last for at least 30 minutes [18]. Thus, we recommend that seizures lasting > 5 minutes should be treated as for status epilepticus[1].

Status epilepticus carries a significant morbidity and mortality and a mortality rate as high as 7% has been reported[2]. Refractory status epilepticus, which can be defined as status epilepticus that fails to respond to a benzodiazepine and a longer acting antiepileptic drug, has been associated with a mortality of up to 16% [2]. The underlying etiology is a more important determinant of outcome than the duration of the seizure. However, in status epilepticus, the prolonged seizure activity *per se* can result permanent brain. Thus, it is important to consider the duration of the seizure prior to onset of treatment and be continuously aware of the duration throughout the treatment.

CONVULSIVE STATUS EPILEPTICUS

Initial management:

Initial management should be directed towards stabilization of airway, maintenance of adequate

ventilation (with oxygen administered as necessary), and circulatory support. Intravenous access should be established immediately and, if that is not achieved after 3 attempts or 90 seconds, intraosseous access should be established.

The initial bloodwork should be directed towards diagnosis of the underlying etiologies, particularly those requiring immediate treatment, such as meningitis, and reversible derangements of metabolism. These should include complete blood count, blood culture (in patients with possible meningitis or encephalitis), electrolytes and glucose. Antiepileptic drug levels should be drawn if the patient is receiving phenobarbital, phenytoin, carbamazepine, or valproic acid.

Drugs

Benzodiazepine

Benzodiazepines act rapidly and are the first-line treatment in status epilepticus. Lorazepam and diazepam are the drugs of choice when there is intravenous access. Rectal diazepam, sublingual lorazepam or buccal midazolam can be administered when IV access cannot be achieved immediately. The dose of benzodiazepine should be repeated after 5 minutes if the seizure continues.

Lorazepam (Ativan)

Intravenous lorazepam has a longer duration of action than diazepam. Intravenous lorazepam has been reported to be associated with more rapid seizure control than IV diazepam in a systematic review of three studies [19]. The recommended dose is 0.1 mg/kg to a maximum of 4 mg per dose. The intravenous formulation of lorazepam can also be administered via the buccal mucosa at a dose of 0.1 mg/kg dose (to a maximum of 4 mg per dose) when IV access is not immediately available but rectal

absorption is erratic (Graves reference).

Diazepam (Valium)

Intravenous diazepam acts within 1-3 minutes of administration. It should be given at a dose of 0.3 mg/kg over 5 minutes (to a maximum dose of 5 mg in infants and 10 mg in children).
Rectal diazepam is absorbed rapidly and attains peak levels in 4-10 minutes. The recommended dose for rectal diazepam is 0.5 mg/kg [5].

Midazolam

Midazolam is a fast-acting, water-soluble benzodiazepine, which is rapidly absorbed via both the nasal and buccal mucosa and can be administered by either route when IV access is not immediately available. The intranasal or buccal dose is 0.2 mg/kg [6, 7]. Midazolam has a short half life (1-12 hours) and must be administered intravenously as an infusion or as multiple small boluses. There are no studies comparing the efficacy of IV midazolam with that of lorazepam or diazepam and its role in the first-line treatment of status epilepticus in children has not been established. However, it is considered to be of particular value in refractory status epilepticus.

<u>Longer-acting antiepileptic medications</u>

Because of the relatively short duration of action of benzodiazepines, a longer-acting antiepileptic drug should be administered, except in febrile children with a seizure lasting less than 15 minutes who respond immediately to a benzodiazepine. Because of the long time required to administer these medications, administration should start *immediately* after the first dose of benzodiazepine. Phenytoin is preferred over phenobarbital because the latter is more likely to cause respiratory depression and to

alter the conscious level of the child, which can complicate assessment in the child when the convulsion has stopped. A smaller dose of phenytoin (5m/kg over 5 minutes) or IV phenobarbital (20mg/kg) should be used in children who are receiving phenytoin prior to the onset of the status. When IV access can not be achieved promptly, IM fosphenytoin or rectal paraldehyde can be given if available.

Phenytoin

Phenytoin is administered at a dose of 18-20 mg/kg intravenously over 20 minutes. It may result in bradycardia, hypotension, and cardiac arrhythmias [5], and cardiorespiratory monitoring is recommended. When IV access is not possible, IM fosphenytoin (18-20 mg/kg/ of phenytoin equivalents over 20 minutes. Alternatively, phenytoin should be administered by the intraosseous route at the same dose and rate as when given intravenously [12].

Phenobarbital

Phenobarbital is administered in a loading dose of 15-20 mg/kg IV. It is highly effective but has a long duration of action. Phenobarbital is more likely than phenytoin to cause sedation, respiratory depression, and hypotension, particularly if a benzodiazpine has also been administered [5].

Paraldehyde

Paraldehyde can be administered rectally in children who fail to respond to IV benzodiazepine and phenytoin therapy, or in children without intravenous or intraosseous access who have not responded to a benzodiazepine. A dose of 0.3-0.5 ml/kg is mixed in an equal amount of mineral or olive oil, to a

maximum total volume of 10 ml.

Further investigations

A CT head scan should be performed after stabilization if the patient has new-onset status epilepticus (especially if there is no obvious cause), no previous history of epilepsy and in refractory status epilepticus[21]

Nonconvulsive status epilepticus (NCSE) may exist when clinical seizure activity has stopped. If the child's level of consciousness does not recover as quickly as expected when the convulsion has stopped or if neuromuscular paralysis is being used to manage the SE, an EEG should be performed. Empiric treatment of NCSE should be instituted if an EEG cannot be obtained.

REFRACTORY STATUS EPILEPTICUS (RSE)

Convulsive status epilepticus that is refractory to a benzodiazepine and phenytoin is associated with a much higher mortality and morbidity [10]. We consider a child to be in refractory status epilepticus if the convulsion continues after administration of a benzodiazepine and an appropriate longer-acting anticonvulsant. There have been no controlled trials on the management of refractory status epilepticus. A recent guideline proposed treatment with a continuous infusion of midazolam, a barbiturate (such as thiopental, pentobarbital, or phenobarbital) or propofol [9]. Treatment requires intubation and cardiorespiratory monitoring, and transfer to an intensive care setting. The management of refractory status epilepticus in children should be performed in consultation with intensive care at BCCH, when these services are not available at the treating institution.

Management

Intubation

Rapid sequence intubation using atropine, ketamine and succinylcholine is recommended prior to treatment with midazolam and is mandatory when using the doses advised for the other drugs.

Eleectroencephalography

There is controversy as to whether both clinical and electrographic seizures require complete control and whether drug dosage should be titrated to achieve a burst suppression pattern or electrocerebral inactivity[21]. In patients treated with pentobarbital or thiopental, persistent seizure control is better and breakthrough seizures occur less often with titration to EEG background suppression than to a burst suppression pattern but hypotension is more common[21].

Drugs

We recommend midazolam as the first-line of treatment because of its relative ease of use and because treatment can be initiated once the airway is appropriately secured. When midazolam doses fail to achieve seizure control, anesthetizing doses of thiopental or propofol should be used. Treatment with either of these drugs requires prior rapid sequence induction, intubation, and ventilatory support

Midazolam

The short-half life of midazolam makes it useful in the treatment of refractory status epilepticus [2]. A loading dose of 0.1 mg/kg is followed by a 2 microgram/kg/minute infusion. This initial infusion rate can be titrated to effect, up to a maximum of 24 micrograms/kg/minute. After prolonged infusions,

midazolam may accumulate in peripheral tissues and result in a prolonged half life up to 50 hours [13, 20].

Barbiturates (Thiopental, pentobarbital)

Thiopental can be administered as a 3-5 mg/kg bolus, followed by additional boluses of 1-2 mg/kg, within 3 to 5 minutes until a clinical response is achieved, up to a maximum total dose of 10 mg/kg. Thereafter, it can be infused at a rate of 3-5 mg/kg/hour [14]**.** Pentobarbital is administered as a 10 mg/kg bolus, followed by a continuous infusion at a rate of 0.5-1 mg/kg/h. After continuous administration, there is a tendency toward accumulation in body tissues, resulting in the need for prolonged ventilatory support even after the withdrawal of medication.

Propofol

Propofol has a rapid onset of action and a short half-life (between 1-2 hours), which permits rapid titration. Prolonged use in children (greater than 48 hours) is associated with an increased risk of propofol infusion syndrome, which is heralded by metabolic acidosis and is characterized by circulatory collapse with rhabdomyolysis, and cardiac arrhythmias [13]. We recommend that it be used with caution in children under the age of 16years and only by specialists with experience in its use. The loading dose is 1 mg/kg; additional 1-2 mg/kg boluses can be administered every 3-5 minutes until a clinical response is achieved, up to a maximum of 10 mg/kg. Continuous infusion, started at an initial rate of 2-4 mg/kg/h, can be titrated to burst-suppression on EEG. The infusion rate should not exceed 4 mg/kg/h and, if seizure control is not achieved rapidly, another agent should be used[14].

Cited References:

1. Appleton R, Choonara I, Martland T, Phillips B, Scott R, Whitehouse W. (The Status Epilepticus

Working Party) The treatment of convulsive status epilepticus in children. Arch Dis Child 2000;83:415-419.

2. Gilbert DL, Gartside PS, Glauser TA. Efficacy and mortality in treatment of refractory generalized convulsive status epilepticus in children: a meta-analysis. Journal of Child Neurology 1999; 14:602-609.

3. Treiman, David M. The role of benzodiazepines in the management of status epilepticus. Neurology. 1990; 4(S2): 32-42.

4. Appleton R, Martland T, Phillips B. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children (review). Cochrane Database of Systematic Reviews 2002 Issue 4. Art No.: CD001905.

5. Livingston, John. Status Epilepticus. In Epilepsy in Children. 2nd Ed. Wallace, Sheila J and Farrell, K., ed. 2004: 290-303

6. Lahat E, Goldman M, Barr J et al. Intranasal midazolam for childhood seizures. Lancet 1998; 352:620.

7. Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. Lancet. 1999; 353: 623-626.

8. Uberall, Michael A. MD; Trollmann, Regina MD; Wunsiedler, Ute MD; Wenzel, Dieter MD. Intravenous valproate in pediatric epilepsy patients with refractory status epilepticus. Neurology. 2000; 54(11): 2188-2189.

9. Meierkord, H, et al. EFNS guideline on the management of status epilepticus. *European Journal of Neurology* 2006; 13:445-450.

10. Mayer SA et al. Refractory Status Epilepticus: Frequency, Risk Factors, and Impact on Outcome. Arch Neurol. 2002; 59:205-210.

11. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. N Engl J Med 1998;339:792–8.

12. Khan TM, Kissoon N, Hasan MY, Saldajeno V, Murphy SP, Lima JJ. Comparison of plasma levels and pharmacodynamics after intraosseous and intravenous administration of fosphenytoin and phenytoin in piglets. Pediatr Crit Care Med. 2000 Jul;1(1):60-64.

13. Rossetti A. Which anesthetic should be used in the treatment of refractory stratus epilepticus? Epilepsia 2007; 48(s8):52-55.

14. Kälviäinen R, Eriksson K, Parviainen I. Refractory generalised convulsive status epilepticus: a guide to treatment. CNS Drugs. 2005;19(9):759-68.

15. Rossetti A et al. Refractory Status Epilepticus: effect of Treatment Aggressiveness on Prognosis. Arch Neurol. 2005; 62:1698-1702.

16. Gilbert DL; Gartside PS; Glauser TA. Efficacy and mortality in treatment of refractory generalized convulsive status epilepticus in children: a meta-analysis. J Child Neurology 1999;14(9):602-9.

17. Claassen J et al. Treatment of Refractory Status Epilepticus with Pentobarbital, Propofol, or Midazolam: A Systematic Review. Epilepsia 2002; 43(2):146-153.

18. Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? Ann Neurol. 2001 May;49(5):659-64.

19. Prasad K, Krishnan PR, Al-Roomi K, Sequeira R. Anticonvulsant therapy for status epilepticus. Br J Clin Pharm. 2007; 63(3): 640-647.

20. Naritoku DK, Sinha S. Prolongation of midazolam half-life after sustained infusion for status epilepticus. Neurology. 2000; 54(6): 1366-1368.

21 Riviello Jr,JJ, Holmes GL. The treatment of status epilepticus. Seminars in Pediatric Neurology. 2004 11:129-138

Other references:

Garr RE, Appleton RE, Robson WJ, Molyneux EM. Children presenting with convulsions (including status epilepticus) to a paediatric accident and emergency department: an audit of a treatment protocol. Developmental Medicine and Child Neurology. 1999; 41:44-47.

Riviello JJ Jr., Ashwal S, Hirtz D, Glauser T, Ballaban-Gil K, Kelley K, Morton LD, Phillips S, Sloan E, Shinnar S. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review). Neurology 2006;67:1542-1550.

Livingston JH. Status Epilepticus. In Epilepsy In Children, 2nd Ed. Wallace SJ and Farrell K. 2004: 290-303.