Clinical review

Status epilepticus: an evidence based guide
Matthew Walker

Writing this article enabled Matthew Walker to revisit the few randomised controlled trials of status epilepticus. This confirmed how poor the data are and that there is little evidence to support one treatment regimen over another.

Status epilepticus is a prolonged seizure of any type. This article focuses mainly on the prolonged convulsion (convulsive status epilepticus) rather than non-convulsive status epilepticus.

Though there is some debate about how long a convulsion has to last before being classified as status epilepticus, 30 minutes is generally accepted. Treatment should begin sooner, however, and a convulsion lasting longer than five minutes, or two convulsions without full recovery of consciousness in between, should usually receive emergency treatment.

Who gets it?
The incidence of status epilepticus is 10-60 per 100 000 person years, with the higher incidences occurring in poorer populations. Half of these patients have convulsive status epilepticus.

Over half the patients with status epilepticus do not have a diagnosis of epilepsy, and often status epilepticus is precipitated by an acute illness. In children, the major cause of status epilepticus is infections accompanied by fever. In adults the major acute causes are:

- Stroke
- Hypoxia
- Metabolic derangements
- Alcohol intoxication or withdrawal (the most common cause in young adults).

In people with a diagnosis of epilepsy, status epilepticus can be precipitated by drug withdrawal, due either to poor concordance or to a doctor stopping the drug.

It is critical to remember that people with epilepsy may have an acute cause for their status epilepticus.

How do I diagnose it?
Diagnosing convulsive status epilepticus is generally straightforward, but it needs to be differentiated from pseudostatus epilepticus (non-epileptic attacks with a psychological basis). Non-epileptic attacks are often prolonged and can be confused with status epilepticus.

In an audit of patients transferred to a specialist neurological intensive care unit for further treatment of their status epilepticus, around half were not in status epilepticus. Instead they were in either pseudo-status or drug induced coma (usually secondary to large amounts of chlormethiazole). Admitting doctors often failed to recognise the possibility of pseudostatus.

You should consider pseudostatus if an episode of status epilepticus does not respond promptly to initial treatment (especially if the seizures are atypical). The clinical features of non-epileptic attacks often include:

- Poorly coordinated thrashing
- Back arching
- Eyes held shut
- Head rolling
- Pelvic thrusting.

Although rises in serum prolactin can be used to differentiate a convulsion from a non-epileptic attack, serum prolactin concentrations are not useful in status epilepticus because they normalise with prolonged seizure activity.

Non-convulsive status epilepticus
Non-convulsive status epilepticus is often difficult to diagnose. As patients in a coma may present no
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**Clinical tip**

Status epilepticus in patients with a history of epilepsy will often resolve if you restart a medication that has been withdrawn or which the patient has not taken. All health professionals who care for patients with epilepsy should ensure that patients do not suddenly stop their medications.

specific clues of seizure activity, all patients in an unexplained coma should have electroencephalography.

In non-comatose patients, non-convulsive status epilepticus can present as confusion, personality change, and even psychosis, with minimal or no clinical clues that there is ongoing seizure activity. Hippus (fluctuations in pupillary size), nystagmus, and cyclidal stereotypical motor manifestations may arouse suspicion. The diagnosis of non-convulsive status epilepticus is therefore critically dependent on the results of electroencephalography. When suspicions are raised, you should refer the patient to a neurologist.

How should I treat it?

Convulsive status epilepticus causes considerable physiological compromise. To prevent potentially fatal complications, as well as giving antiepileptic drugs, you should start treatment:

- Giving oxygen
- Monitoring and maintaining blood pressure
- Replacing fluids
- Giving glucose (if you suspect hypoglycaemia) in combination with high potency thiamine (250 mg, for example as the parenteral formulation Pabrinex) in patients likely to have poor nutrition.

People who do not respond to first line treatment (see below) will need to be transferred to an intensive care unit.

Drug treatment varies according to stage:

- Premonitory stage—increasing numbers of seizures often precede convulsive status epilepticus. Treatment at this stage is usually successful and prevents status epilepticus and its associated morbidity and mortality
- Established status epilepticus—this stage needs emergency intravenous treatment
- Refractory status epilepticus—this stage needs intensive care management.

The drugs proposed for use in status epilepticus include clonazepam, clomethiazole, and valproate. But they have not been tested satisfactorily in randomised controlled trials and can’t be recommended currently in management protocols.

**Diazepam**

**Benefit**

You can use diazepam by rectal route in the premonitory phase or as first line treatment intravenously during the established stage. Rectal diazepam will stop recurrent seizures in around 70% of patients. Intravenous diazepam will terminate status epilepticus in 60-80% of patients.

Although diazepam has a long elimination half life of less than 30 minutes. This short plasma half life leads to a rapid fall in plasma levels and a 50% chance of seizures recurring within two hours.

**Side effects**

Side effects of diazepam are:

- Sedation
- Respiratory depression
- Hypotension.

Respiratory depression is largely unreported in randomised studies of rectal diazepam in acute seizures. In a study comparing intravenous diazepam, intravenous lorazepam, and placebo for out of hospital treatment of status epilepticus, placebo was associated with twice as many complications (hypotension, cardiac dysrhythmias, or respiratory intervention). This suggests that ongoing status epilepticus is likely to have greater cardiorespiratory complications than benzodiazepine treatment.

**Evidence**

Three randomised studies have compared rectal diazepam with placebo for the treatment of recurrent seizures, and one compared rectal diazepam with buccal midazolam. They showed that rectal diazepam is more effective than placebo and as effective as midazolam. No serious complications were reported.

A study of 205 patients with more prolonged seizures (> 10 minutes) in the community found that intravenous diazepam and intravenous lorazepam were more effective than placebo at preventing the evolution to or continuation of status epilepticus. There is no evidence for determining how intravenous diazepam compares with rectal diazepam in the community.

Five randomised studies of status epilepticus have compared diazepam alone or in combination with phenytoin against lorazepam, phenytoin and phenobarbitalone, intramuscular midazolam; or lorazepam, phynotin, and phenobarbitalone. These studies have not established that diazepam is superior to any other regimen, nor does diazepam result in significantly greater side effects than any other treatment regimen.

**Dose**

Rectal diazepam should be given at a dose of 10-20 mg (rectal gel). Intravenous diazepam should be given at a dose of 10-20 mg at 2 mg/min.

**Lorazepam**

**Benefit**

You should use intravenous lorazepam as first line treatment during the established stage. Intravenous lorazepam will terminate status epilepticus in 60-90% of patients.

Lorazepam may be preferable to diazepam as first line treatment because of its longer redistribution half life, leading to a smaller chance of recurrence of seizures. This has not been evaluated in a randomised controlled trial. The randomised studies that have looked at this question were inadequately powered to detect a significant difference.

**Side effects**

Side effects of lorazepam are:

- Sedation
Side effects of midazolam are:

- Respiratory depression
- Hypotension.

In a study comparing intravenous diazepam, intravenous lorazepam, and placebo for out-of-hospital treatment of status epilepticus, placebo was associated with twice as many complications (hypotension, cardiac dysrhythmias, or respiratory intervention). This suggests that ongoing status epilepticus is likely to have greater cardiorespiratory complications than benzodiazepine treatment.

Evidence

In an out of hospital study of 205 patients with prolonged seizures (>10 minutes), intravenous diazepam and intravenous lorazepam were more effective than placebo at preventing the evolution to or continuation of status epilepticus.

Three randomised studies of lorazepam use for status epilepticus compared lorazepam with diazepam and lorazepam with phenytoin and diazepam, phenytoin alone, and phenobarbitone. They established that lorazepam is superior to phenytoin alone and can be given more rapidly than regimens containing phenytoin or phenobarbitone. Lorazepam did not cause significantly greater side effects than the other drugs tested.

Dose

Intravenous lorazepam should be given at a dose of 4 mg at 2 mg/minute.

Midazolam

Benefit

Midazolam given by the buccal route in the premonitory phase has a 75% chance of preventing further seizures. In early stages it can be given intramuscularly when intravenous access is difficult to attain. There are also reports supporting its use as a continuous infusion in refractory status epilepticus.

Side effects

Side effects of midazolam are:
- Sedation
- Respiratory depression
- Hypotension.

When midazolam was given by the buccal route, no clinically important adverse events were noted in a small randomised trial.

Evidence

The randomised trials of the efficacy of midazolam were carried out in children, and care must be taken when extrapolating these data to adults.

Buccal midazolam has been compared with rectal diazepam in children with serial seizures in a randomised study. No significant difference between these two drugs was found, but the study investigated 79 episodes in only 28 patients, and almost half the episodes occurred in only two patients.

Intramuscular midazolam was compared with intravenous diazepam in a small study (24 patients) in children with motor seizures lasting longer than 10 minutes. Efficacy did not differ significantly, but intramuscular midazolam was more quickly administered because of difficulties getting intravenous access. Nasal midazolam has been suggested as an alternative route, but there are no randomised controlled trials.

Dose

Buccal or intramuscular midazolam should be given at a dose of 10 mg.

Phenytoin

Benefit

Phenytoin should be given in established status epilepticus as an adjunct to a benzodiazepine. Around half the patients who have not responded to the initial benzodiazepine will respond with the addition of phenytoin.

Side effects

Side effects of phenytoin are:
- Sedation
- Respiratory depression
- Hypotension
- Rash
- Purple glove syndrome (danger of extravasation).

Blood pressure and electrocardiogram need to be monitored during phenytoin infusions. Giving phenytoin alone, rather than with diazepam, does not reduce the risk of respiratory depression. The phenytoin produg fosphenytoin reduces the small risk of purple glove syndrome (ischaemia of the hand).

Evidence

One randomised study compared lorazepam, phenytoin alone, phenytoin and diazepam, and phenobarbitone in status epilepticus. Phenytoin alone was the least effective of the drugs at stopping status epilepticus, and the only significant difference in efficacy was between lorazepam and phenytoin alone.

No randomised controlled data supporting phenytoin as a second line treatment are available, but one uncontrolled study suggested that 50% of patients not successfully treated with a benzodiazepine would respond to a second line treatment (usually phenytoin).

In purple glove syndrome a blue-purple discoloration appears around the intravenous site two to 12 hours after phenytoin has been given, followed by oedema and, in some cases, necrosis. A prospective study found an incidence of purple glove syndrome of 1.7%, which probably does not justify the widespread use of fosphenytoin (a water soluble produg of phenytoin that does not cause purple glove syndrome).

Phenobarbitone

Benefit

Phenobarbitone can be given in established status epilepticus: it gives a 60-70% chance of stopping the status epilepticus.
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Side effects

Side effects of phenobarbitone are:
- Sedation
- Respiratory depression
- Hypotension
- Rash

Reports that the combination of phenobarbitone and a benzodiazepine can lead to cardiorespiratory compromise, along with concerns about its hypoten-
sive and respiratory depressant effect, mean that phenobarbitone is used less commonly as a first line
treatment. These opinions are not supported by
randomised controlled trials, which suggest that side
effects with phenobarbitone are no greater than with
other regimens.25

Evidence

Two randomised studies compared phenobarbitone
with diazepam against lorazepam, phenytoin alone, or
diazepam and phenytoin.15,24 These studies established
that phenobarbitone is as efficacious as other regimens
tested and does not result in significantly greater side
effects.

Dose

Intravenous phenobarbitone should be given at 10-20
mg/kg at 100 mg/minute.

Refractory status epilepticus

If the status epilepticus continues despite a benzo-
diazepine and an adequate loading dose of phenytoin,
then management should take place on the
intensive care unit, with anaesthesia to control the epi-
leptic activity. In addition to anaesthesia, antiepileptic
drug treatment should continue. You should monitor
the patient with an electroencephalograph at least
once a day.

Anaesthesia can be induced by barbiturate or non-
barbiturate drugs. Several anaesthetics have been
recommended; the most commonly used anaesthetics
are the intravenous barbiturates thiopentone and
phenobarbitone, the intravenous non-barbiturate prop-
ofol, and continuous midazolam infusion.15,24

No randomised controlled trials have compared
these treatment options. A meta-analysis of reports of
these treatment regimens showed no difference in
terms of mortality, but that pentobarbital was slightly
more effective than midazolam, at the expense of
greater hypotension.25 These data need to be
interpreted with caution because the studies were not
randomised, had different outcome measures, and had
considerable reporting bias (the reports are mostly
retrospective). Propofol and midazolam have
pharmacokinetic advantages over the barbiturates,
which readily accumulate in fat and muscle, leading to
prolonged action after stopping the infusion.

What tests should you do?

Tests in patients with status epilepticus are used to help
with management and identify the cause. In all
patients, you should take blood urgently for analysis of
- Glucose
- Blood gases
- Renal function
- Liver function
- Calcium and magnesium concentrations
- Full blood count
- Blood clotting measures
- Anticonvulsant concentrations.

It is often useful to store blood for further
investigation, including tests for illicit drugs.

Electrocardiography, blood pressure, and blood gas
monitoring are usually necessary. Other investigations
depend on the clinical circumstances. The ranges of
causes of status epilepticus determine the investiga-
tions required.

Emergency computed tomography is needed in
most circumstances. Magnetic resonance imaging and
examination of cerebrospinal fluid are also often
necessary, depending on clinical circumstance.

When should I refer my patient?

Patients with suspected non-convulsive status epilep-
tic should be referred to a neurologist, and all patients
with status epilepticus that has not responded to first
treatment (benzodiazepine and phenytoin) should
be referred to a neurologist for further management.

What’s the outlook?

The prognosis for convulsive status epilepticus is poor,
with a mortality of 10-20%.25 The risk of cognitive
Teaching the teacher a lesson

As senior lecturer in the Department of Anaesthesia at Malawi’s medical school, I am responsible for organising a three-week module in anaesthesia and intensive care medicine for the fourth year medical students. I quickly abandoned any unrealistic goal for complete coverage of our syllabus in the eleven days that remained of our module, after loss to bank holidays and funerals for complete coverage of our syllabus in the eleven days that remained of our module, after loss to bank holidays and funerals remained of our module, after loss to bank holidays and funerals (one local and one in Rome). I designed a module to show our wide variety of subspecialty interests and to give the students some relevant practical skills of use in their future roles as interns.

I felt that things were progressing fairly well until the second Friday of the module. As I was starting the introduction to the section on intensive care medicine, I was stopped by the appearance of a letter from the second row of the class. I was told I should read the letter, which had been signed by all 24 students, on 19 July 2002 by guest. Protected by copyright. http://www.bmj.com/ BMJ: first published as 10.1136/bmj.331.7518.673 on 22 September 2005. Downloaded from

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