Pre-hospital and emergency department treatment of convulsive status epilepticus in adults: an evidence synthesis

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Declared competing interests of authors: Lorna Aucott is a member of the National Institute for Health Research Public Health Research funding committee (February 2017–present).

Published March 2022
DOI: 10.3310/RSVK2062

Scientific summary

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Health Technology Assessment 2022; Vol. 26: No. 20
DOI: 10.3310/RSVK2062

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Scientific summary

Background

Status epilepticus is the most severe form of epilepsy; it is a life-threatening neurological condition that requires urgent treatment. Status epilepticus can be convulsive (i.e. with limb stiffness, abnormal posturing and jerking, so called tonic–clonic seizures, often with impaired awareness/consciousness) or non-convulsive (altered consciousness with little or no limb movements) and can be of focal or generalised onset. The focus of this study is generalised convulsive status epilepticus, defined as either $\geq$ 5 minutes of continuous seizure activity or two or more discrete seizures between which there is no full recovery of consciousness.

Status epilepticus arises because of the failure of mechanisms that abort seizure activity, that is either the breakdown of the mechanisms that terminate seizures or the instigation of mechanisms responsible for abnormally sustained seizures. In adults, the most common causes of status epilepticus are low levels of antiepileptic drugs in people with existing epilepsy, cerebrovascular diseases, metabolic abnormalities, alcohol-related causes and hypoxia. Status epilepticus can occur equally in people with no history of epilepsy or in people with established epilepsy. The incidence of status epilepticus has been reported as 10–60 per 100,000 population per year, with half of these people having convulsive status epilepticus. The incidence of status epilepticus is equal in males and females.

Status epilepticus is a medical emergency with significant morbidity and mortality that can worsen with suboptimal or delayed treatment. It has been shown that early treatment of status epilepticus is associated with better outcomes in terms of seizures terminated on arrival at the hospital emergency department and reduced morbidity and mortality. Therefore, the main goal of the treatment of status epilepticus is to promptly stop both clinical and electroencephalographic seizure activity.

The first-line treatment of status epilepticus is currently benzodiazepines, a class of drugs that bind the gamma-aminobutyric acid receptor complex that modulates gamma-aminobutyric acid release in the central nervous system and causes down-regulation of neuronal excitation (i.e. neurons become less excitable). In the community, buccal midazolam is recommended as the first-line treatment for prolonged or repeated seizures, or rectal diazepam can be administered if preferred or if buccal midazolam is not available. Intravenous lorazepam can be administered if intravenous access is already established and resuscitation can be facilitated. In addition, care plans outlining the home use of buccal midazolam or rectal diazepam are recommended for people who have had a previous episode of prolonged or serial convulsive seizures. At present, there is a lack of clarity about the optimal treatment of convulsive status epilepticus in the pre-hospital setting.

Objectives

The purpose of this assessment was to conduct a synthesis of the current evidence on the clinical effectiveness and cost-effectiveness of treatments for adults with generalised convulsive status epilepticus in emergency department and pre-hospital settings to inform clinical practice and future research.

Methods

This assessment was conducted according to current methodological standards. Comprehensive searches were conducted to identify reports of randomised controlled trials (RCTs) assessing pre-hospital treatments

of status epilepticus in adults. Major electronic databases were searched, including MEDLINE, EMBASE, PsycInfo®, CINAHL and CENTRAL, with no restrictions on date or language of publication. Final searches were carried out on 21 July 2020. The population of interest was adults (aged ≥ 16 years) with convulsive status epilepticus who were attended out of hospital by non-medical staff (e.g. caregivers) or paramedics, or received their first-line treatment at arrival at the hospital emergency department. Primary outcomes of interest were seizure cessation [measured in terms of either the number of people with cessation of seizure activity within 5–15 minutes of drug administration (or any designated period of time as specified by the trial investigators) or the time to seizure cessation from the time of drug administration], recurrence of seizure [measured in terms of either the number of people with recurrence of seizures within a designated period (probably 12 hours) or the time from seizure cessation to recurrence] and adverse events (namely respiratory depression and 30-day mortality). Secondary outcomes included the need for additional drugs to stop seizure (within 12 hours), the need for hospital admission, length of stay in intensive care unit, 6-month mortality, time to return to baseline function (3–6 months), health-related quality of life and the number of people requiring an emergency call-out (among those attended out of hospital by non-medical staff). Data were extracted by two reviewers independently. The Cochrane Risk of Bias tool (version 2) was used to assess the risk of bias of the included RCTs.

A review of economic evaluations of first-line pre-hospital or emergency department treatments for adults with status epilepticus was also carried out. Searches focused on MEDLINE, EMBASE, NHS Economic Evaluation Database, Health Technology Assessment Database, Research Papers in Economics, and the ISPOR Scientific Presentations Database, with no restriction on date, language or publication type.

Results

Clinical effectiveness

Four trials, with a total of 1345 randomised participants, of whom 1234 were adults, were included in the review of clinical effectiveness. Two trials at a low risk of bias showed that benzodiazepines were effective for the treatment of status epilepticus in the pre-hospital setting. In particular, one trial showed that more participants treated with either 2 mg of intravenous lorazepam or 5 mg of intravenous diazepam had termination of seizure on arrival at the emergency department than those receiving intravenous placebo (59.1%, 42.0% and 14.3% of participants in the lorazepam, diazepam and placebo groups, respectively) and one trial showed that pre-hospital treatment with 10 mg of intramuscular midazolam was as effective as treatment with 4 mg of intravenous lorazepam in adults with convulsive status epilepticus (seizures were absent in 73.4% and 63.4% of participants in the intramuscular midazolam and intravenous lorazepam groups, respectively; $p < 0.001$ for inferiority and for superiority).

Furthermore, one trial at low risk of bias showed that the addition of 2.5 g of levetiracetam to 1 mg of clonazepam did not result in higher rates of seizure cessation, compared with 1 mg of clonazepam alone, although both combinations were successful in stopping seizures (73.5% and 83.8%, respectively). Another trial at a high risk of bias showed that seizures were terminated in a larger proportion of participants who received 100 mg/minute intravenous phenobarbital plus 40 mg/minute phenytoin (72.2%) than in those treated with 2 mg/minute intravenous diazepam plus 40 mg/minute optional phenytoin (33.3%). Across trials, the median time to seizure cessation from administration of study drug ranged from 1.6 minutes for intravenous lorazepam to 15 minutes for intravenous diazepam plus phenytoin.

Two trials at a low risk of bias reported the number of people with recurrence of seizures; frequencies were similar between treatment arms of each individual trial (10.4% for levetiracetam plus clonazepam vs. 19.1% for placebo plus clonazepam in one trial, and 11.4% for intramuscular midazolam vs. 10.6% for intravenous lorazepam in the other trial). Respiratory depression was reported by three trials at a low risk of bias and was generally low across the active treatment arms of individual trials (from 6.4% for intramuscular midazolam to 10.6% for intravenous lorazepam). In one trial, which included a placebo arm, respiratory depression was reported in 15.5% of placebo-treated participants.

Similarly, low mortality rates were reported by three trials at a low risk of bias, assessed as the number of deaths between enrolment and discharge from hospital. Levels of mortality ranged from 2% to 7.6% for intravenous lorazepam across the active treatment arms and from 6.2% to 15.5% across the placebo arms. In two trials with a low risk of bias, the reported proportion of participants admitted to hospital ranged from 47.8% (for intravenous diazepam) to 65.6% (for intravenous lorazepam). One trial reported a median length of stay in intensive care unit of 3 days for each treatment group (levetiracetam plus clonazepam and placebo plus clonazepam), whereas another trial reported a mean length of stay in intensive care unit of 4.1 and 5.7 days for the two treatment groups (intramuscular midazolam and intravenous lorazepam, respectively).

Cost-effectiveness

Only one study met the broad definition of economic evaluation as specified in the inclusion criteria for the review of economic evaluations, but another two cost-of-illness studies were also assessed. The included economic evaluation compared lorazepam (4 mg intravenously, repeated up to two times) with diazepam (10 mg intravenously, repeated up to three times) in adults with convulsive status epilepticus who received treatment in a teaching hospital in London. The evaluation used data from 72 patients treated with lorazepam ($n = 17$) or diazepam ($n = 55$) who were identified from medical records. The evaluation was limited in scope and considered only the first-line treatment acquisition costs in relation to the outcome of seizure cessation (without need for second-line treatment). The study found that lorazepam was associated with a higher likelihood of treatment success than diazepam (9/17 doses lorazepam vs. 14/55 doses diazepam; $p = 0.042$) and was associated with a lower chance of recurrence. Although the cost of lorazepam was higher than the cost of diazepam, the average cost per successful outcome was no different between the two treatments (£1.47 vs. £1.46). The study is limited by the small numbers, the retrospective observational design and the limited scope of the costing. With respect to the cost-of-illness studies reviewed, these showed that time to effective first-line treatment with any benzodiazepine was a key determinant of the duration of the status epilepticus episode, the clinical outcomes from treatment, the duration of hospital stay and the associated treatment costs.

Limitations

We identified only a limited number of trials assessing the use of antiepileptic drugs for the pre-hospital treatment of status epilepticus in the adult population. A statistical synthesis of relevant outcome data was considered inappropriate because of the differences in terms of treatment comparisons and choice and definition of outcome measures across the identified trials.

Apart from one trial that compared intramuscular midazolam with intravenous lorazepam, all the remaining trials assessed the use of antiepileptic drugs administered intravenously. We have not identified any RCTs assessing the use of buccal midazolam or rectal diazepam, which are currently recommended by clinical guidelines.

The review of economic evaluations was hindered by the lack of suitable data.

Conclusions

Clinical effectiveness

Evidence from individual trials at a low risk of bias indicates that benzodiazepines are effective for the pre-hospital treatment of convulsive status epilepticus in adults. In particular, intravenous lorazepam and intravenous diazepam administered by paramedics are more effective than placebo, and intramuscular midazolam is non-inferior to intravenous lorazepam. The addition of levetiracetam to clonazepam does not offer clear advantages over clonazepam alone.

Cost-effectiveness

Based on a review of the available clinical and economic evidence, the key clinical outcomes (and associated resource use) that should be captured in economic evaluations of pre-hospital or emergency department treatments for adults with convulsive status epilepticus should include cessation of seizure activity, time to seizure cessation, requirement for second-line treatments, recurrence of seizures, length of stay in hospital and intensive care unit admissions. For economic evaluation comparing low-cost benzodiazepine drugs, it is plausible that more effective treatments will dominate less effective treatments over the course of a treatment episode if these treatments reduce the use of second-line treatments, intensive care unit admissions and/or the length of stay in hospital. If higher-cost first-line treatments become available in the future, where short-term episode cost-savings are not sufficient to fully offset increased medicine acquisition costs, a model using the outcome of cost per quality-adjusted life-year over a longer time horizon would be preferable. Such a model could, in theory, capture the potential longer-term health benefits of reducing the duration and severity of status epilepticus episodes and associated sequelae.

Suggested research priorities

- Large well-designed clinical trials are needed to compare the use of intravenous lorazepam versus intravenous diazepam and to confirm the efficacy and safety of intramuscular midazolam compared with intravenous lorazepam administered by paramedics at the scene in the community or on arrival at the emergency department.
- It is also necessary to establish which is the most effective and preferable treatment that caregivers could administer at the scene prior to the arrival of paramedics. Future clinical trials comparing buccal and intranasal midazolam with rectal diazepam would provide useful information to inform the pre-hospital management of patients, especially when intravenous/intramuscular access is not feasible.
- Future clinical trials should also aim to establish optimal doses of benzodiazepines used as first-line treatments in the pre-hospital setting.
- Future research is needed to show which first-line treatment is most cost-effective and which mode of administration is preferable.
- Harmonisation of outcome measures would be useful to facilitate future clinical research.
- Information on adherence to current clinical guidelines with regard to the pre-hospital treatment of status epilepticus would be useful.
- Research aiming at understanding the underlying pathophysiology of treatment response in adults with status epilepticus would be useful to inform future treatment development.
- High-quality economic evaluations are required to determine the value for money of different drug treatments for convulsive status epilepticus and their modes of administration.

Study registration

This study is registered as PROSPERO CRD42020201953.

Funding

This project was funded by the National Institute for Health Research (NIHR) Evidence Synthesis programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 20. See the NIHR Journals Library website for further project information.

Health Technology Assessment

HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

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This report

The research reported in this issue of the journal was commissioned and funded by the Evidence Synthesis Programme on behalf of NICE as project number NIHR132153. The contractual start date was in July 2020. The draft report began editorial review in January 2021 and was accepted for publication in May 2021. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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