Status epilepticus: Practice variation and adherence to treatment guideline in a large community hospital

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ABSTRACT

Purpose: To evaluate the treatment of status epilepticus (SE) and adherence to treatment guideline in a large Finnish community hospital.

Materials and methods: A consecutive series of 137 patients treated in the emergency department of Kuopio University Hospital. Enrollment took place between March 23 and December 31, 2015. Pediatric patients and postanoxic seizures were excluded. The Finnish Status Epilepticus Current Care Guideline was used as the evaluation benchmark.

Results: Seventeen patients recovered spontaneously. First-line treatment was given to 108 patients with 35.2% efficacy. Second-line treatment was given to 81 patients with 87.7% efficacy. Six patients with refractory SE received successful third-line treatment and four were excluded from intensive care because of futility. The starting dose of a first-line drug was lower than the lowest therapeutic dose in 37.0% of the patients. The escalation from first- to second-line treatment took longer than 60 min in 55.1% of the 70 patients who received both treatments. The first loading dose of a second-line drug was markedly low (<80% of the recommended dose) in 26.2% of the 81 patients treated with second-line drugs.

Conclusions: Prompt and effective pharmacotherapy is the cornerstone of good SE treatment. Subtherapeutic doses of first-line benzodiazepines should be avoided. Benzodiazepine-resistant SE must be recognized early to facilitate rapid treatment escalation. The quality of second-line treatment suffers from excessive delays and inadequate weight-based dosing of antiseizure medications.

1. Introduction

1.1. Background

Status epilepticus (SE) is a neurological emergency that manifests as a prolonged epileptic seizure or seizure cluster with incomplete recovery between the seizures [1]. SE patients are at a high risk of neurologic and systemic complications; therefore, treatment guidelines have been developed to facilitate early and effective treatment [2–4]. The treatment aims to stop seizure activity before irreversible cerebral damage occurs, hence reducing mortality, morbidity, and the risk of subsequent epilepsy [5]. According to the International League Against Epilepsy, emergency treatment of SE should commence at 5 min in tonic-clonic seizures, at 10 min in focal seizures with impaired consciousness, and at 10–15 min in absence seizures [6].

There are three different lines of antiseizure medications (ASMs) used to treat SE [7]. The standard treatment consists of first-line benzodiazepines and second-line intravenous antiseizure drugs. Patients who do not respond to these lines of treatment have refractory SE (RSE) and may benefit from third-line treatment with anesthetic drugs in the neurologic intensive care unit [7]. In frail and multimorbid patients, withholding intensive care should be considered if the expected outcome is survival with severe functional impairment and limited life expectancy at best [8].

Prior studies have identified some key problems in delivering optimal SE treatment. Recognizing SE can be delayed, especially in nonconvulsive seizures [9]. Even after SE is recognized, the delay before giving effective drug treatments may be remarkably long, which is associated with worse outcomes [10,11]. In first-line treatment, the practice of giving multiple small benzodiazepine doses has been...
reported, and it may explain inadequate seizure control and delayed second-line treatment in some patients [12,13]. Achieving seizure control promptly with first- and second-line drugs is the key to minimize seizure duration, prevent RSE, and avoid complications of third-line therapy, which translates to better outcomes [14,15].

1.2. Aim of study

We evaluated the treatment of SE and adherence to the corresponding Finnish Current Care Guideline [4] in emergency patients admitted to a large Finnish community hospital. The emphasis was on the use of ASMs: timing, doses, and efficacy. Our main objective was to identify and tackle the obstacles to optimal SE treatment, based on prospective observation of a real-life patient cohort. A secondary objective was to study the few RSE patients who could not be given intensive care but were assigned to palliative care instead – a subgroup of patients that we identified in our earlier study on the outcomes of SE [16].

2. Material and methods

2.1. Design

Adult patients (≥16 years of age) matching the operational definition of SE were prospectively recruited in the emergency department (ED) of Kuopio University Hospital between March 23 and December 31, 2015. A consecutive patient series was created. The operational definition of SE was adopted from the Finnish Current Care Guideline [4]: a prolonged (>5 min) epileptic seizure, a seizure cluster (≥2 seizures) with no interictal recovery to neurologic baseline, or a recurrent tonic-clonic seizure (≥3 discrete seizures within any 24 h). Patients with postanoxic seizures were excluded. Only one enrollment was allowed for each patient.

2.2. Setting

The study site is the central community hospital of the North Savo Hospital District in Eastern Finland. It provides the only round-the-clock emergency neurology service for a population of 248,000. Paramedics and emergency physicians operate in the area with 24 ambulances and an emergency medical helicopter. Additionally, there are two regional hospitals in the area that provide round-the-clock access to general practitioners but limited diagnostic and treatment options in neurologic emergencies.

2.3. Data collection and analysis

We used medical records and structured forms filled in by emergency medical personnel to collect the data. Descriptive statistics were used to characterize the patients and features of the seizure episodes. The seizure type was determined by clinical signs before treatment with ASMs. Seizures that couldn’t be controlled with second-line drugs were classified as RSE. The cessation of SE was determined on clinical grounds or by EEG in nonconvulsive seizures. The duration of seizure, latency to treatment, and length of hospital stay were recorded. If seizure onset was not witnessed, the duration was measured from the moment the patient was found. In recurrent tonic-clonic seizures, by our operational definition, the onset of third seizure marked the beginning of SE. The data on treatment delay and outcomes in this cohort have been published previously [10,16].

ASMs choices and their timing, dosing and efficacy were registered. A drug treatment was considered effective if it successfully stopped the SE and the seizure did not recur during surveillance in the ED. All aspects of pharmacotherapy were evaluated for adherence to the Finnish Current Care Guideline of SE [4]. Fig. 1 shows the guideline-recommended timeframes, ASMs and their dosing, and the usual place of treatment at each stage of SE. The guideline is highly compatible with the respective guidelines of the Neurocritical Care Society (NCS) [2] and the American Epilepsy Society (AES) [3].

The Research Ethics Committee of the hospital district approved the study design. The hospital district permitted the use of medical records in accordance with Finnish legislation. Statistical software (SPSS 27, IBM Corp, New York) was used to process data. All tests were two-sided, and statistical significance was set at p < .05.

3. Results

3.1. Study cohort

There were 137 SE patients who fulfilled our inclusion criteria in the ED during the study period. Their mean age was 59.5 years (range = 16–92, SD = 18.1). The majority were male (62.8%). As many as 65.7% had a previous epileptic seizure in their medical history, and 49.6% had a diagnosis of epilepsy. The most common comorbidities were psychiatric disorders (34.3%), alcohol abuse (33.6%), cerebrovascular disease (29.9%), and dementia (22.6%). Do-not-resuscitate orders were in effect for 24.1% of the patients. Fourteen patients were readmitted for SE during the study period but were enrolled only once.

3.2. Features of the SE episodes

The most common SE type was tonic-clonic (94 episodes, 68.6%), followed by focal seizure with impaired consciousness (20 episodes, 14.6%) and focal aware seizure (14 episodes, 10.2%). Myoclonic, absence, and nonconvulsive comatose seizures were rare. The etiology followed by focal seizure with impaired consciousness (20 episodes, 14.6%) and focal aware seizure (14 episodes, 10.2%). Myoclonic, absence, and nonconvulsive comatose seizures were rare. The etiology was acute symptomatic in 53 episodes (38.7%), where the leading causes were abrupt withdrawal from alcohol or ASM. Only few patients had a potentially fatal acute symptomatic etiology (cerebrovascular accident in six, central nervous system infection in two, and head trauma in one patient). Thirty-six (26.3%) episodes had a cryptogenic etiology. The remaining 48 episodes had either a remote or a progressive symptomatic etiology and were commonly caused by past cerebrovascular accidents, degenerative brain diseases, and brain tumors.

The course of SE was continuous in 96 episodes (70.1%) and a seizure cluster in 32 episodes (23.4%). A recurrent tonic-clonic seizure...
was encountered in nine episodes (6.6%). The median duration of SE was 2 h 30 min, with 67.9% of the episodes lasting longer than 60 min. The duration was less than 30 min in 20.4% and 30–60 min in 11.7% of the episodes. Ten episodes of RSE (7.3%) were seen. The longest SE that ended with recovery lasted 73 h 51 min. The median length of hospitalization was 2 d 6 h, ranging from a 2 h visit to the ED to three weeks of care in the neurological ward, excluding subsequent rehabilitation in a health center. The outcome at one month after SE was known for 120 patients (87.6%). The mortality rate was 10.0%.

3.3. Treatment course

Fig. 2 depicts the course of treatment of all 137 SE patients. First-line treatment was given to 108 patients (78.8%). The total efficacy of first-line treatment (including first-line drug combinations) was 35.2%. Seventy-one first-line treatments (65.7%) were started out-of-hospital. Twenty-nine SE patients were transferred to hospital before the initiation of first-line treatment. In eight patients, the onset of SE and the initiation of first-line treatment occurred in the ED. Second-line drugs were given to 81 patients (66.1%): a single ASM to 59 patients, two ASMs to 16 patients, three ASMs to five patients, and four ASMs to one patient. The total efficacy of second-line treatment (including second-line drug combinations) was 87.7%. Third-line treatment with propofol was given to six RSE patients (4.4%); it stopped the seizure in all. On average 2.0 (range = 1–3, SD = 0.6) second-line drugs were administered before third-line treatment.

In 29 SE episodes (21.2%), no guideline-recommended benzodiazepine drug was used. Seventeen SE episodes (12.4%) resolved spontaneously. Seven patients (5.1%) were currently seizure-free but had suffered a reoccurring tonic-clonic seizure; therefore, a loading dose of a second-line drug was given in accordance with the Current Care Guideline. In two cases, direct second-line treatment was given to a patient with a long-lasting focal seizure. Nonstandard treatment was given to three patients: One patient was given IV midazolam (MDZ) and subsequently levetiracetam (LEV). Two patients received oral diazepam (DZP) mixture to stop a reoccurring tonic-clonic seizure; the other needed fosphenytoin (FOS) treatment shortly thereafter, the other had an uneventful recovery.

Four patients with RSE (2.9%) were excluded from third-line treatment because of futility and received combinations of second-line drugs instead.

3.4. Pharmacotherapy

The frequency, latency, and efficacy of the different drugs in the three lines of treatment are summarized in Table 1. IV DZP was the preferred initial drug both in- and out-of-hospital (N = 80). First-line treatment was started with buccal MDZ in 16 patients and with rectal DZP in 10 patients. IV DZP and buccal MDZ showed efficacies of 32.5% and 25.0% in stopping the SE, respectively. The efficacies did not differ between the two treatments, \( \chi^2 (1, N = 96) = 0.35, p = .77 \). All patients treated with rectal DZP needed further treatment. IV lorazepam (LZP) and IV clonazepam (CLZ) were both used once as the initial therapy with 100% efficacy. Six patients treated with rectal DZP received follow-up treatment with IV DZP with 50.0% efficacy. Ten patients who had no response to buccal MDZ received follow-up treatment with IV DZP with 20.0% efficacy. One patient who had no response to IV DZP received follow-up treatment with IV LZP, which stopped the seizure.

In second-line treatment, FOS was the preferred ASM. It was the initial second-line drug of 59 patients with 66.1% efficacy. LEV was initially given to ten patients with 80.0% efficacy. Valproate (VPA) was initially given to 12 patients with 75.0% efficacy. There were no statistically significant differences in the efficacies of FOS, LEV, and VPA as the first-second-line ASM, \( p = .69 \). Lacosamide (LCM) was combined to the second-line treatment of one RSE patient, but to no effect.

In third-line treatment, propofol was used in all six patients. Two cases of super-refractory SE were seen where a longer than 24 h anesthesia was needed before the seizure subsided. In four cases of RSE, Table 1

| First drug given from each line of treatment: frequency, latency, and efficacy. | N | Latency (t, median) | Efficacy (%) |
|---|---|---|---|
| First-line treatment | 108 | 40 min | 32.5 |
| DZP IV | 80 | 55 min | 32.5 |
| MDZ BUCC | 16 | 20 min | 25.0 |
| DZP PR | 10 | 15 min | 0.0 |
| LZP IV | 1 | 15 min | 100.0 |
| CLZ IV | 1 | 1 h 56 min | 100.0 |
| Second-line treatment | 81 | 2 h 40 min | 66.1 |
| FOS | 59 | 2 h 26 min | 66.1 |
| LEV | 10 | 2 h 45 min | 80.0 |
| VPA | 12 | 3 h 23 min | 75.0 |
| Third-line treatment | 6 | 6 h 0 min | 100.0 |
| PPF | 6 | 6 h 0 min | 100.0 |

DZP, diazepam; MDZ, midazolam; LZP, lorazepam; CLZ, clonazepam; FOS, fosphenytoin; LEV, levetiracetam; VPA, valproate; PPF, propofol.

Fig. 2. Flow chart of the treatment of 137 status epilepticus patients. BZD, benzodiazepine.
clobazam was administered via nasogastric tube as an add-on drug. LCM was used twice during anesthesia as an add-on drug. The maximally treated patient suffered a 38 h 32 min long SRSE and was given DZP, FOS, LEV, VPA, propofol, clobazam, and LCM.

3.5. Adherence issues

Various issues with adherence to the treatment guideline were recognized. The most common problem was excessive treatment delay (>30 min to first-line or >60 min to second-line treatment from the moment the operational criteria of SE are met). A time stamp was available for the beginning of first- and second-line treatment in 100.0% and 98.8% of the treated patients, respectively. First-line treatment was delivered within 30 min to 40.7% of the treated patients. Only 15.0% of the second-line treatments were started within 60 min. The escalation from first- to second-line treatment was generally slow and took longer than 60 min in 55.1% of the 70 patients who received both treatments.

The choice and dosing of benzodiazepines was variable. IV DZP was the first benzodiazepine drug of 80 patients (Fig. 3). IV LZP and IV CLZ were both the initial drug of one patient. Of the 82 patients treated with IV benzodiazepines, the treatment was started at a lower-than-recommended dose in 36 (43.9%), necessitating dose repetitions to cumulatively reach the lowest therapeutic dose. A lower-than-recommended starting dose was given to 1/10 (10.0%) patients treated with rectal DZP and to 3/16 (18.8%) patients treated with buccal MDZ. Overall, 37.0% of the benzodiazepine starting doses were low. Overdosing of first-line drugs did not occur with IV LZP, IV CLZ, or any formulation of DZP. One patient received a higher-than-recommended starting dose of buccal MDZ.

The dosing of the second-line drugs was difficult to evaluate because weight was documented in only 51.9% of the patients treated with these ASMs. The following mean loading doses of the initial second-line drugs could be calculated: FOS 17.8 mgPE/kg (N = 30, range = 11.5–25.0, SD = 3.0), VPA 10.8 mg/kg (N = 5, range = 9.4–12.1, SD = 1.0), and LEV 18.1 mg/kg (N = 7, range = 12.5–26.6, SD = 5.4). A significantly lower than recommended (<80%) loading dose was noted in eleven patients (three patients treated with FOS, five patients treated with VPA, and three patients treated with LEV). Extrapolated to the whole cohort, the initial loading dose of a second-line drug could be low in 26.2% of the patients. Overdosing occurred in three patients treated with FOS (>120% of the recommended loading dose). Maintenance doses were not ordered in the ED for 12.3% of the patients who received second-line treatment.

3.6. Palliatively treated patients

Four patients (2.9%) were treated palliatively because of RSE and a poor prognosis. They received first-line treatment and two to four different second-line drugs to no effect. The patients’ ages ranged from 55 to 92. Their seizures were caused by intracerebral hemorrhage, degenerative brain disease, previous brain injury, and abrupt ASM withdrawal. All palliatively treated patients had at least one characteristic that decreases the likelihood to benefit from intensive care: a severe comorbid condition, poor baseline function, or living in an institutional care facility.

4. Discussion

In this prospective study, we evaluated treatment aspects in a cohort of 137 SE patients. We report spontaneous cessation in 12.4% and success rates of 35.2% for first-line therapy and 87.7% for second-line therapy. All six intensive care–treated patients who received third-line therapy (4.4%) survived; four patients were assigned to palliative care (2.9%). Our study shows that a substantial number of patients do not receive guideline-recommended care. Dosing errors and delayed treatment are the most common problems. Because of our relatively small cohort size and the complex interplay of the factors determining the outcome of SE [17], we cannot tell whether guideline violations affected the prognosis of our patients. Nevertheless, a body of evidence supports the implementation of guideline-based treatment to improve patient outcomes [12,18].

Early and sufficient dosing of a first-line drug is needed to achieve the guideline-recommended therapeutic dose within the given 30 min timeframe. The neurobiological model of established SE supports this practice: Prolonged seizures are known to become benzodiazepine-resistant [19]. To save time and maximize efficacy, the therapeutic dose should be given as a single dose whenever possible. Underdosing of benzodiazepines, or failure to initiate drug treatment altogether, are frequent problems during the early treatment of SE [20,21]. In our cohort, 43.9% of the starting doses of an IV benzodiazepine drug were lower than the lowest guideline-recommended dose. Of the 100 patients whose SE started out-of-hospital and who received first-line treatment, only 71% received prehospital benzodiazepine treatment. Even the noninjectable benzodiazepine drugs were occasionally used in lower-than-recommended doses. Overestimation of the risk of cardiorespiratory depression may explain these findings, yet it should not lead to insufficient treatment [20,22]. Educational efforts are needed to change the practice of benzodiazepine undertreatment. Obviously, home prescriptions for the noninjectable benzodiazepine drugs must be for the correct dose.

The optimal first-line drug choice has been under intense investigation. Our national guideline currently recommends rectal DZP, buccal MDZ, IV DZP, or IV LZP for all types of seizures and IV CLZ as an alternative for myoclonic SE. The use of intranasal MDZ with an atomizer is guideline-supported too, although not routine practice at the time of this study. If venous access is not easily obtainable, we prefer buccal MDZ over rectal DZP because of easier administration and possibly better efficacy [23]. If venous access is readily available, we prefer IV LZP over IV DZP because of longer duration of action and possibly better efficacy [22,24], which may both contribute to seizure control and eliminate the need of dose repetitions.

New first-line treatment options will probably be integrated into our national guideline in the future. The challenge is to preserve the guideline’s practicality and emphasis on early treatment. IM MDZ is already promoted by the guidelines of NCS [2] and AES [3]. We acknowledge the evidence supporting its’ use [25] and our emergency medical personnel may already use it when an IV access is not available and severe trismus blocks the buccal route. Additionally, the role of nonbenzodiazepine drugs as part of the first-line treatment requires evaluation. It has been postulated that better urgent control of SE could be achieved by reinforcing first-line treatment with other drug classes. Preliminary evidence suggests that IV brivaracetam, a fast-acting ASM, could be used for this purpose: Pharmacologically, it has synergistic action with the conventional benzodiazepine drugs, and it may even work as a benzodiazepine substitute [26].

We are concerned about the long second-line treatment delay (2 h 40 min) in our cohort. We investigated treatment delays in our earlier paper [10] and now found evidence that slow treatment escalation is a major source of delay. In more than half (55.1%) of the patients who required transition from first- to second-line treatment, this escalation took longer than 60 min, which is longer than the guideline-recommended timeframe for second-line treatment. During this treatment step, first-line treatment is continued simultaneously with the patient’s hospital transfer. Subsequent monitoring in the ED. Confronted with partial treatment response, the clinician may continue with benzodiazepine administration and close patient surveillance. Second-line treatment has to be initiated promptly once a benzodiazepine-resistant SE is recognized. This could be upon hospital arrival if adequate prehospital treatment has been given: a prenotice by paramedics is recommended in such cases. Second-line treatment delay could be minimized by bringing second-line drugs to the field to be administered by ambulance crews. In the SAMUKeppra study, IV LEV was used during prehospital treatment.
Fig. 3. The number of doses, cumulative dose, and starting dose of intravenous diazepam as the initial first-line drug in status epilepticus. DZP, diazepam.
In clinical practice, the choice of the initial second-line drug appears to be guided mostly by personal preference. No adequately powered and well-designed study has demonstrated the superiority of any individual ASM for benzodiazepine-resistant SE. The available evidence suggests that the guideline-recommended drugs have comparable efficacy, while VPA and LCM may cause less cardiorespiratory depression [28]. Hence, it would seem reasonable to prefer either VPA or LCM in patients who have received large doses of benzodiazepines or who are at risk of cardiorespiratory collapse because of a co-existing medical condition.

The doses of the second-line drugs are often calculated based on crude weight estimates. Seizure patients are unable to disclose their weight and are not routinely weighed in the ED either. Missing weight data undermines our ability to reliably analyze the dosing of the second-line drugs. However, we estimate that the initial second-line drug could be underdosed in up to 26.2% of the patients. Underdosing seemed more prevalent with VPA and LEV than with the more commonly used FOS. All the VPA doses that we could calculate were suboptimal, but higher VPA doses were given in some cases with missing weight data. To optimize therapy, dosing charts should be readily available wherever treatment decisions are made. The electronic health records should have a clearly defined space for weight and notifications for if it is missing or outdated. The loading doses of FOS 20 mg/PE/kg, VPA 40 mg/kg and LEV 60 mg/kg were used in the ESETT study [29], showing comparable safety and efficacy. These doses are consistent with the AES treatment algorithm [3] and markedly higher than in our guideline. The clinician who uses a more conservative guideline should appreciate this information when deciding on the loading dose of a patient whose precise weight is unknown.

As the population ages, there will be more multimorbid and frail SE patients with limited capacity to benefit from intensive care. Early and effective treatment with first- and second-line drugs is crucial when third-line treatment is not an option. Aggressive prehospital treatment may also decrease the number of hospitalizations [8]. Six of our patients received third-line treatment for RSE and survived, but four patients with RSE were excluded from intense care and treated palliatively instead. The clinician should know that in some cases of RSE, he/she must consider withholding intensive care and simultaneously coordinate combination treatment with second-line drugs. New effective and well tolerated add-on drugs with different mechanisms of action are urgently needed especially for patients with RSE. Clobazam and LCM were occasionally used for RSE in our cohort. Perampanel, an AMPA antagonist, apparently has some desirable features of a good add-on drug, but its role in the treatment of SE is still unclear [30].

There are limitations to this single-center study. Our cohort size is small with much heterogeneity in seizure types, etiologies, and treatments. For this reason, subgroup analyses were often not feasible. We probably missed some patients who were treated in the two smaller hospitals of our area, most for cases that stopped spontaneously or responded quickly to treatment and patients who had do-not-hospitalize orders and were assigned to palliative care. Thus, our study may underestimate their number. Finally, the pharmacotherapy of SE is evolving rapidly. After these study data were collected, changes in pharmacotherapy have likely occurred, and our results may not accurately reflect the most recent treatment practice.

5. Conclusion

The care of SE patients can be improved by correcting the deviations from the treatment guidelines that were identified in this study. First-line benzodiazepines are 35.2% effective in stopping the SE, but they are started in subtherapeutic doses in one-third of the patients, and their repeated dosing slows down the escalation to second-line treatment. Combinations of different second-line drugs have up to 87.7% efficacy. The use of second-line drugs needs to be based on weight-based dosing and the latest evidence from clinical trials. Treatment algorithms should be made for patients who present with RSE and who are not candidates for third-line treatment.

Abbreviations

| Acronym | Full Form |
|---------|-----------|
| SE      | status epilepticus |
| ASM     | antiseizure medication |
| RSE     | refractory status epilepticus |
| ED      | emergency department |
| NCS     | Neurocritical Care Society |
| AES     | American Epilepsy Society |
| MDZ     | midazolam |
| DZP     | diazepam |
| LZP     | lorazepam |
| FOS     | fosphenytoin |
| VPA     | valproate |
| LEV     | levetiracetam |
| LCM     | lacosamide |
| STP     | sodium thiopental |
| PPF     | propofol |
| BZD     | benzodiazepine |
| CLZ     | clonazepam |

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Author Contributions

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Data curation: JS.
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Funding acquisition: JS, HH, RK.
Visualization: JS.
Writing - original draft: JS, AMK, HH, and RK.
Writing - review & editing: JS, AMK, HH, and RK.

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