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Treatment adherence and outcomes in the management of convulsive status epilepticus in the emergency room

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ABSTRACT – *Purpose.* According to published literature status epilepticus (SE) is associated with 7-39% mortality. Timely management is one variable that potentially influences the outcome. We sought to review the process of acute management of SE at the University of Alberta Hospital and correlate outcome with adherence to a recommended treatment protocol.
Methods. We identified 86 patients 18 years of age or older who presented with convulsive SE to our emergency room between 2000 and 2004. We defined SE as continuous convulsive activity for 30 or more minutes or ≥ 2 convulsions with incomplete recovery in the interim. Information was collected pertaining to etiology, epidemiology, and management. We then reviewed the relationship of the treatment protocol in terms of mortality and morbidity.
Results. Forty five patients were included. There were 18 males and 27 females with a mean age of 45 years; 80% were known to have epilepsy. Subtherapeutic drug levels were found in the majority 60%; benzodiazepines (diazepam 81% and lorazepam 19%) were the first line agent in 93.3% mostly initiated by paramedics (EMS); 48.9% of patients required intubation and 26.7% required admission to intensive care. Four patients died. Control of convulsive SE was obtained sooner for patients in whom therapy was administered according to the recommended time frame ($p \leq 0.02$).
Conclusion. The presence of strict treatment protocols for SE made readily available for the treating staff could potentially improve the outcome of patients. Despite the lack of standardized treatment protocols among various physicians, most patients are treated according to generally recommended sequence and time frames. Analysis of this data will help devise prospective treatment protocols.

Key words: status epilepticus, management, protocol, sequence, time frame

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Status epilepticus (SE) is a well recognized neurological emergency; its treatment has been well established in the literature. The recommended treatment strategies however are continuously reviewed by multidisciplinary experts whose aim is to maximize the use of best evidence in the diagnosis and treatment of SE and to improve patient outcomes. In the U.S. there are 150 000 new cases annually (DeLorenzo *et al.* 1995), and the incidence is independent of gender (DeLorenzo *et al.* 1996).

SE can have devastating consequences for patients. For example, the short

term mortality for all age groups ranges between 7-39% (Knake *et al.* 2001, Vignatelli *et al.* 2003, Chin *et al.* 2004). In adults, the long term mortality for those with an underlying cause of SE is age dependent, ranging from 17% in those under 65 to 76% after 65 years of age (Logroscino *et al.* 2002). Morbidity from SE is unclear. In animal models, memory deficits and learning disabilities, as well as overt neuronal injuries, have been demonstrated (Holmes *et al.* 2002); however, clinically significant cognitive decline has not been demonstrated (Adachi *et al.* 2005). Children with prolonged febrile convulsions have been shown to have enlarged hippocampal volumes (Scott 2002, 2003). In animal studies, experimental seizures can lead to epilepsy without necessarily leading to obvious structural alterations (Koh *et al.* 1999).

Strict treatment protocols for SE are available; however, there is evidence that these are not practiced universally. While some centers are aggressive in the management of this condition, they do not have an accepted chronological sequence of treatment. It is still uncertain whether following a particular treatment protocol in terms of choice of medications, vigilance of administration, and respiratory management with intubation independently influences patient outcomes. Our study sought to address these issues in detail.

The main goal of this project was to review the current practice in the management of SE at an inner city Canadian Emergency Department (ED), by assessing the differences in management between patients who did and did not receive recommended care and correlate this with their subsequent outcomes. This evaluation was designed to determine whether the adherence to a fixed treatment protocol could improve the outcome, as well as provide a background for future prospective evaluations of SE treatment and protocol formation.

Methods

Design

This was a retrospective chart review of all patients 18 years or older presenting to the emergency department with status epilepticus between January 2000 and October 2004.

Setting

The study was conducted at the University of Alberta Hospital (UAH), a tertiary care ED in Edmonton, Alberta. This 650-bed hospital has a referral Neurosciences program and its ED manages approximately 70 000 adult and pediatrics patients annually. It is staffed with full-time certified and fellowship trained emergency physicians and has Canada's largest Emergency Medicine residency program. The population of Edmonton is 920 000.

Patients

All ED patient charts are coded by specially trained medical records nosologists using the International Classification of Diseases (ICD), Version 10. Patients were included if they were identified by ICD-10 codes as one of the following: "*Grand mal* status" (3453), "*Grand mal* status" (G410), "Status epilepticus unspecified" (G419), or "Other status epilepticus" (G418). SE was subsequently defined as a seizure in the form of continuous motor activity for ≥ 30 minutes, or ≥ 2 convulsions with out return to baseline consciousness (DeLorenzo *et al.* 1996). Multiple encounters from the same patient were counted separately.

Data extraction

The diagnosis of SE was reconfirmed by the authors to ensure it met the above definition during chart review and disagreement by reviewers was resolved by consensus. Each patient encounter started from the time of the first assessment by an intervening service either by an Emergency Medical Service (EMS) team if called to the scene or by a physician in the emergency room. The time of SE onset was identified from the documentation. Note was also taken of specific management offered at the discretion of the treating service which included the administered drugs, the agent that halted the seizure, the sequence of drug administration, the time frame in which interventions occurred, number of agents required, duration of SE, intubation, Intensive Care Unit (ICU) admission, specific investigations performed (CT, MRI, EEG, and CSF analysis) and their results, and of the specialty service consulted. Status type was classified as either convulsive or subtle SE, and clinical epileptic activity as either continuous or intermittent. Patients who did not display clear epileptic activity (e.g.: no motor activity or occasional muscle twitches) but showed electrographic SE on EEG were considered to have subtle status epilepticus.

Interventions

The recommended agents, sequence of drug administration, and the time frames of management offered to patients were compared with the corresponding components of the Epilepsy Foundation of America (EFA) guidelines for the management of SE (DeLorenzo *et al.* 1993) *(table 1)*. A comparison was then made of outcomes between patients whose management fell within EFA guidelines and the patients whose management didn't. Demographics were collected with regard to sex, age, and etiology, as was information regarding outcome considering short-term morbidity, mortality, and duration of hospital stay.

Duration of hospital stay was addressed from triage time to discharge or death.

Causation

Etiology was classified depending on whether this was the first epileptic event in a patient from a structural, hypoxic,

Table 1. A suggested timetable for the treatment of status epilepticus (Courtesy of JAMA August 18, 1993;270 No. 7: 854-859. Copyright © 1993; American Medical Association. All rights reserved).

Time (min)	Action
0-5	Diagnose status epilepticus by observing continued seizure activity or one additional seizure.
	Give oxygen by nasal cannula or mask; position patient's head for optimal airway patency; consider intubation if respiratory assistance is needed.
	Obtain and record vital signs at onset and periodically thereafter; control any abnormalities as necessary; initiate ECG monitoring.
	Establish an IV; draw venous blood samples for glucose level, serum chemistries, hematology studies, toxicology screens, and determinations of antiepileptic drug levels.
	Assess oxygenation with oximetry or periodic arterial blood gas determinations.
6-9	If hypoglycemia is established or a blood glucose determination is unavailable, administer glucose; in adults, give 100 mg of thiamine first, followed by 50 mL of 50% glucose by direct push into the IV line; in children, the dose of glucose is 2 mL/kg of 25% glucose.
10-20	Administer either lorazepam, 0.1 mg/kg IV at 2 mg/min, or diazepam, 0.2 mg/kg IV at 5 mg/min. If diazepam is given, it can be repeated if seizures do not stop after 5 minutes; if diazepam is used to stop the status, phenytoin should be administered next to prevent recurrent status.
21-60	If status persists, administer 15-20 mg/kg of phenytoin, no faster than 50 mg/min in adults and 1 mg/kg/min in children by IV; monitor ECG and blood pressure during the infusion; phenytoin is incompatible with glucose-containing solutions; the IV line should be purged with normal saline before the phenytoin infusion. Alternatively, fosphenytoin, 20 mg/kg phenytoin equivalents at 150 mg/min in adults or 3 mg/kg/min in children, can be used.
> 60	If status does not stop after 20 mg/kg of phenytoin, give additional doses of 5 mg/kg to a maximal dose of 30 mg/kg.
	If status persists, give phenobarbital, 20 mg/kg IV at 100 mg/min; when phenobarbital is given after a benzodiazepine, the risk of apnea or hypopnea is great, and assisted ventilation usually is required.
	If status persists, give anesthetic doses of drugs such as phenobarbital or pentobarbital; ventilatory assistance and vasopressors are virtually always necessary.

Time starts at seizure onset. Note that a neurological consultation is indicated if the patient does not wake up, convulsions continue after the administration of a benzodiazepine and phenytoin, or confusion exists at any time during evaluation and treatment.
ECG: Electrocradiogram, IV: Intravenous line.

inflammatory, substance related, or metabolic cause. For patients who were known to have epilepsy (two or more previously unprovoked epileptic seizures or those taking antiepileptic medications for seizures), the etiologies included sub therapeutic antiepileptic drug levels, metabolic, inflammatory, and those with no clear provoking causes.

The cessation of SE was determined by the time of last documentation of clinical epileptic activity, unless there was EEG evidence of subtle SE or recurrence of seizure which required anticonvulsant treatment. Death or any medical complication (cardiovascular, respiratory, metabolic, neurological, and infectious) that arose during, or within 30 days of the presentation was considered to be related to SE and/or its treatment. Exclusion was made of patients with treatment commenced in a peripheral center then transferred to the UAH emergency, a high suspicion of non-epileptic events, < 18 years, and those who did not meet the study definition of SE.

Statistical analysis

Data are presented as proportions, means (with standard deviation [SD]), or medians (with interquartile range [IQR]). The association between duration of seizures and other factors were examined using Chi-squared test, Student's t-test, and Kruskal-Wallis rank test, as appropriate. All p-values are two-tailed, with $p < 0.05$ considered statistically significant.

Results

Sample

Overall, 86 patient encounters were registered in the medical records; eight charts were not available for review. From the 76 available charts, 22 patients did not meet our definition for SE. Nine were treated in a peripheral hospital and then transferred to our center, therefore excluded for not receiving emergency management at UAH. Two encounters were considered non-epileptic events. Thus, 45 encounters were included in this review.

Demographics

The mean age was approximately 49. Eleven patients (24.4%) were over 65 years of age. There were 18 males and 27 females. Thirty eight patients arrived to the emergency *via* EMS. All of the 45 cases of SE showed overt epileptic activity and one progressed to subtle SE. It was the first seizure for nine (20%) patients, and the remaining 36 (80%) were known to have epilepsy. All of the patients

in the first seizure group had their SE manifest with intermittent convulsive activity, while in the patients known to have epilepsy, 26 (74.3%) had intermittent convulsive activity, and nine (25.7%) had continuous convulsive activity. In over half of the encounters 25 (55.6%) the status was secondarily generalized.

Etiologies

Most patients (36; 80%) had a previous history of seizures and 21 (55.6%) of these had sub-therapeutic antiepileptic drug (AED) levels. Eleven (30.55%) had an unclear etiology, and four (11.1%) had a metabolic cause. In the group that had no previous seizure history, five had a structural etiology (e.g.: stroke, space occupying lesion, or demyelinating plaque), two were substance-induced, two remained unknown after all investigations, and one was due to metabolic derangement.

Evaluations

Investigations were commonly performed, with CT head (68.9%), EEG (37.8%), and CSF analysis (11.1%) being most common. The CT was normal in nine (29%) of the 31 scanned patients, showed a new structural lesion in three (9.7%), and a known structural lesion in 19 (61.3%).
In the 17 who had an interictal EEG performed, eight (47.1%) had generalized slowing, four (23.5%) had lateralized epileptiform discharges, three (17.6%) were normal, and two (11.8%) had generalized epileptiform discharge. One of the latter two was diagnosed with subtle SE.

Duration of SE

The duration of SE was determined to range from 30 minutes to four days (median 72 min). The median time to initial assessment by a treating staff (e.g., EMS member, ED physician, or specialist) was 13.5 minutes (IQR: 8, 24.25), while the median time to hospital triage was 50 minutes (IQR: 37.5, 72.75). The median duration of hospital stay was three days (IQR: 0.88, 5).

Agents

The most frequently used first line agents were the benzodiazepines (diazepam and/or lorazepam) in 42 [93.3% (34 diazepam and 8 lorazepam)], phenytoin was used most commonly as the second line agent [29 (64.4%)]. Other benzodiazepines, propofol, phenobarbital, and thiopental were used as third and fourth line agents at similar frequencies *(figure 1)*. All SE patients treated with phenytoin whose weight was recorded (n = 27) received doses lower than 20 mg/kg.

Response to treatment

With regard to control of SE, 20 patients (44.4%) ceased seizing after administration of the first line agent, 17 (37.8%) after the second line agent, five (11.1%) after the third, and one (2.2%) required a fourth line agent. Two (4.4%) patients died without achieving control of SE, one received three agents and the other received four.

Outcomes

Overall, 22 (48.9%) patients were intubated; 12 (26.7%) were admitted to Intensive Care Unit (ICU). Most [25 (55.6%)] had SE > 60 min; 32 required > one therapeutic agents, seven (15.5%) required > two therapeutic agents. Various medical complications were seen; overall, 17 (37.8%) patients suffered a complication and four (8.9%) died. Of the 22 patients requiring intubation, 16 (35.6%) were intubated with neuromuscular blocking agents. The neurology service was the first consulted service for 35 (77.8%) patients, Intensive care for two (4.4%), and neurosurgery for one (2.2%). Seven (15.6%) were solely treated by the ED staff.

Compliance with approach

Overall, 32 (71.1%) patients received the recommended order and sequence of treatment compared to 13 (28.9%) who were not treated according to sequence. Comparing these two groups, outcomes (morbidity and mortality, duration of hospital stay, need for intubation, and duration of SE) were similar. Patients who were managed within the recommended time frames seized for a significantly shorter time (median: 38 *versus* 95 minutes) than those whose management duration fell outside the time frame (p = 0.02; *table 2*).

Discussion

This report identified and examined the cases of SE seen at a Canadian tertiary care emergency referral centre and identified several important conclusions.
First, using *a priori* and accepted definitions, SE was rarely seen over a 4.5-year study period. Despite seeing over 300,000 patients during this period, this ED encountered only 45 patients with a confirmed diagnosis of SE. We considered "patient encounters" when reviewing charts (n = 45), as some patients had presented more than once with SE. Since more than 40% of cases were eliminated after further review, use of medical records data would result in an overestimation of the problem. This further suggests that results from administrative data on this topic should be viewed with caution.
Second, SE remains a very serious and potentially fatal disease; it is associated with the need for intubation in approximately 50% of the cases and complications are common.
Third, while the general approach among emergency physicians appears to be to use benzodiazepines +/- phenytoin, variability in care is seen and standardization should be a priority. Finally, despite the small sample, we were

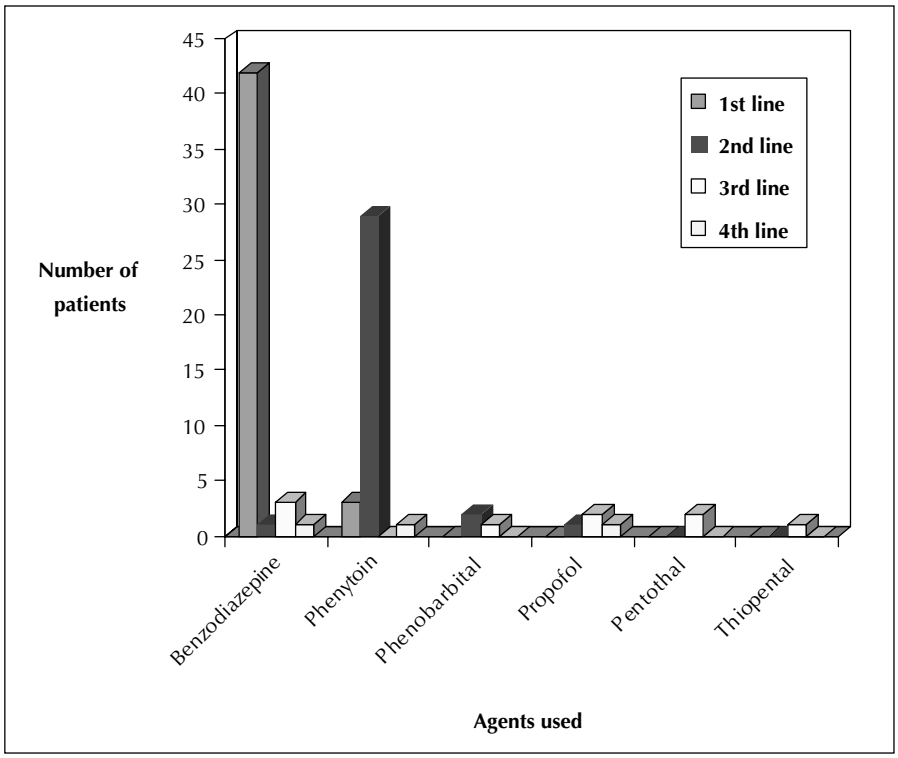

Figure 1. Sequence of agents used according to preferred line of therapy.

able to identify a relatively strong association between rapid treatment and cessation of the seizure.

SE in the Emergency Department

Although there is a likely variation among centers, emergencies pertaining to seizures are estimated to represent 0.5 -1.2% of all ED visits (Reuber *et al.* 2000, Huff *et al.* 2001). In one multi-center review, which looked at seizures in the ED in both adults and children, SE was seen in 6%. They also assessed the number of seizure patients who had CT (35%), lumbar puncture (6%), and EEG (3%) (Huff *et al.* 2001). It is quite likely that these resources were more often utilized in SE patients. In a separate review of epilepsy related emergencies in the ED, it took approximately 30 minutes to reach medical attention for SE patients (Pellock *et al.* 2004), and in this review, a median time of 50 minutes until triaged in a hospital. Indicating that aggressive treatment will likely be needed since the condition has lasted this duration (Walton *et al.* 1988, Kapur and MacDonald, 1997, Treiman *et al.* 1998, Lowenstein *et al.* 1999, Eriksson, 2005). This can be effectively carried out with a treatment protocol (Eriksson *et al.* 2005, Pang and Hirsch, 2005) and facilitated by family education as well as EMS training (Pellock *et al.* 2004).

There seems to be more literature that addresses protocol guidance *versus* the variability of approaches among phy-

Table 2. Outcome of patients compared with treatment according to recommended time frame.

	Not managed within time* (n = 30)	Managed within time* (n = 15)	P value
Mortality and morbidity	13 (43%)	7 (50%)	0.75
Hospital stay (days)	2 (0.3, 4)	4 (2, 6)	0.07
Intubated	15 (50%)	7 (47%)	0.99
SE duration from 1st assessment (median minutes and ranges)	**95 (59, 156)**	**38 (28, 62)**	**0.02**

* "Managed/not managed within time" refers to whether the intervention was administered according at the recommended time from the onset of SE as per EFA guidelines.

Table 3. Sequelae of patients with status epilepticus.

Sequelae	
Status > 60 minutes	25 (55.6%)
Required > 1 line of therapy	32 (71.7%)
Required > 2 lines of therapy	7 (15.5%)
Required Intubation	22 (48.9%)
Admitted to ICU	12 (26.7%)
Medical Complications	17 (37.8%)
Progressed to NCSE	1 (2.22%)
Death	4 (8.9%)

sicians when managing children in the ED (Martland *et al.* 1998, Garr *et al.* 1999, Reuber *et al.* 2000). In the pediatric groups, implementation of therapeutic protocols and adherence to time frames improves the quality of emergency care and patient outcome in up to 94% of cases (Shephard, 1994, Garr *et al.* 1999, Singhi, 2003). Despite these differences, the acquired study demographics, etiologies, and outcomes appear similar to past reports (Bassin *et al.* 2002).

The commonly accepted definition of refractory status epilepticus (RSE) is SE duration ≥ 60 minutes that does not respond to a benzodiazepine nor to the addition of the minimum required dose of either phenytoin or phenobarbital (Classen *et al.* 2001, Mayer *et al.* 2002,). The eight (17.8%) patients that required more than two lines of therapy fall under this group, as their SE lasted > 60 minutes. Some authors have recommended a tighter definition of RSE, such as failure of one or two standard therapies regardless of seizure duration (Bleck, 2005). The number of patients that fall into either definition are shown *(table 3)*; the incidence (at 30-50%) reported here is similar to previously published data (Mayer *et al.* 2002).

Almost half of the intubated patients required ICU admission, the other half was successfully extubated in the ER within hours. Currently there are no explicit recommendations for the type or dose of neuromuscular blocking agent when intubating patients in SE, and the time for intubation is guided according to clinical criteria (e.g.: level of consciousness, airway protection, and respiratory and hemodynamic stability).

We can infer from our review that a detailed protocol that emphasizes judicious and timely administration of AEDs is a component of SE management that has the potential to shorten the duration of SE. Previous work supports this, as we now know that the longer the duration of SE, the more difficult it becomes to control (Walton *et al.* 1988, Kapur and MacDonald, 1997, Treiman *et al.* 1998, Eriksson, 2005), and that symptomatic epilepsy develops significantly more often following RSE than non-refractory SE (Holtkamp *et al.* 2005). The pre-hospital treatment trial of SE showed that regardless of treatment, patients in SE at emergency department arrival were much more likely to require intensive care unit admission than those whose seizures were terminated in the out-of-hospital environment (73% *versus* 32%) (Lowenstein *et al.* 2001).This is also the case in children (Alldredge *et al.* 1995). In addition, the response rate to the second conventional agent is much better if given early in the course of SE (Bleck, 2002, Mayer *et al.* 2002). Even lower than standard doses of lorazepam, given early in the course, can terminate 60% of SE episodes within 10 minutes (Alldredge *et al.* 2001, Bleck, 2002). Finally, protocols for other commonly encountered disorders in the ER (such as asthma, stroke and pneumonia) have helped improve patient outcomes in many hospitals. One approach would be to implement treatment protocols within the Emergency Medical Services (EMS) and the ED with a clear focus on the prompt and timely administration of optimal doses of medication, particularly first and second line agents.

Limitations

There are a number of limitations in our study that warrant discussion: first, its retrospective methods result in missing data. Second, the sample size was small and represented only the population of a single tertiary care referral center with the only epilepsy department in northern Alberta, where there is a tendency to receive unique epilepsy patients. Third, the coding may have introduced bias as well as lead to neglecting proper clinical seizure classification by the treating physician. In fact, we suspect that the great majority of the seizures were secondarily generalized. The decision to use the 30 minute cut off instead of other durations (e.g., SE definition of five minutes duration has been suggested more recently (Lowenstein *et al.* 1999)) was critical. For example, the majority of patients who were excluded for the < 30 minute criteria would have met the shorter duration criteria. The time it took patients to reach medical attention from the onset of SE varied, therefore we took into account the duration of treatment from the first assessment by a treating faculty

member as the variable to assess the effect of the protocol. The benefit of timely administration of drugs was significant despite the duration of SE prior to receiving medical attention. Lastly, there was a lack of ictal EEG evaluation in almost all of these patients. Although shortage of manpower precludes an optimal use of EEG, this procedure can significantly contribute in the prompt diagnosis and management (Lowenstein and Alldredge, 1998).
We had predicted including a larger number of SE patients in this review and therefore deduce that had we reviewed the charts of all patients with a diagnosis of seizures and epilepsy this number would have been significantly higher. Thus, we believe that the numbers identified by our study is an underestimation resulting from inconsistent or suboptimal coding, and suspect that patients who had SE may have been admitted under different diagnostic codes.

Conclusion

Status epilepticus is an uncommon condition seen in the emergency department yet it is associated with complex treatments and interventions, frequent complications, and a high death rate. The main conclusion of our study is that variability in practice could be reduced and aggressive managements could improve outcomes. This can be achieved by a set and approved treatment protocol available to all treating physicians in a medical facility. More research on this important topic should be encouraged. □

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