Management and prognosis of status epilepticus according to hospital setting: a prospective study

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Summary

Background: The treatment of status epilepticus (SE) is based on relatively little evidence although several guidelines have been published. A recent study reported a worse SE prognosis in a large urban setting as compared to a peripheral hospital, postulating better management in the latter. The aim of this study was to analyse SE episodes occurring in different settings and address possible explanatory variables regarding outcome, including treatment quality.

Methods: Over six months we prospectively recorded consecutive adults with SE (fit lasting five or more minutes) at the Centre Hospitalier Universitaire Vaudois (CHUV) and in six peripheral hospitals (PH) in the same region. Demographical, historical and clinical variables were collected, including SE severity estimation (STESS score) and adherence to Swiss SE treatment guidelines. Outcome at discharge was categorised as "good" (return to baseline), or "poor" (persistent neurological sequelae or death).

Results: Of 54 patients (CHUV: 36; PH 18), 33% had a poor outcome. Whilst age, SE severity, percentage of SE episodes lasting less than 30 minutes and total SE duration were similar, fewer patients had a good outcome at the CHUV (61% vs 83%; OR 3.57; 95% CI 0.8–22.1). Mortality was 14% at the CHUV and 5% at the PH. Most treatments were in agreement with national guidelines, although less often in PH (78% vs 97%, P = 0.04).

Conclusion: Although not statistically significant, we observed a slightly worse SE prognosis in a large academic centre as compared to smaller hospitals. Since SE severity was similar in the two settings but adherence to national treatment guidelines was higher in the academic centre, further investigation on the prognostic role of SE treatment and outcome determinants is required.

Key words: treatment; guidelines; duration; outcome

Introduction

Status epilepticus (SE) occurs yearly in at least 10/100 000 people in central Europe [1, 2] and is related to considerable morbidity and mortality [3]. Whilst its prognosis is essentially related to underlying aetiology and age [4, 5], it remains unclear if and to what extent pharmacological treatment influences SE outcome. Clinical studies focusing on SE treatment are rare and their quality is considered poor. A 2005 Cochrane review identified only eleven publications reaching valid conclusions regarding initial treatment [6]: lorazepam appears superior to diazepam or phenytoin [6]. Current European therapeutic recommendations are mostly based upon expert opinion [7–10]. In most guidelines, SE management is based on a three-step approach, starting with benzodiazepines, followed by classical antiepileptic drugs (mostly phenytoin, valproate, phenobarbital), and finally pharmacological coma induction with an anaesthetic agent (barbiturates, propofol, or midazolam) [3, 10]. Coma induction is indicated for patients with SE resistant to the first two steps. In view of potential risks related to both treatment and prolonged mechanical ventilation and

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immobilisation, it may be advisable to balance the risks and benefits of this therapeutic approach [11, 12], especially in patients with potentially less dangerous forms of SE [13]. Given the paucity of evidence-based data, clinicians often manage SE patients as they feel best, generating divergent treatment "schools" [12].

A recent retrospective Italian study suggested that SE prognosis in adults varies according to hospital type and location: a peripheral rural hospital had a lower thirty-day mortality in comparison too a large academic urban centre (7% vs 33%) [14]. However, an epidemiological survey conducted ten years ago in French-speaking Switzerland showed a relatively low mortality in both urban (7%, Geneva) and rural regions (12%, Valais). A recent study on convulsive SE from Ethiopia reported a case fatality of 20% [15], which appears broadly comparable with SE mortality in western countries, in spite of a greater latency to diagnosis and the lack of intravenous AED formulations and raises the possibility that SE treatment might have a relatively limited impact.

The goal of this study was to determine how SE episodes are managed and if SE treated in a large urban hospital has a different prognosis as compared to regional or district hospitals. Furthermore, possible explanations were addressed, including referral bias and, in view of the increasing popularity of therapeutic guidelines in various clinical settings, treatment quality.

Methods

Design, participating hospitals, patients and SE definition

This is a prospective exploratory case series of adults with SE conducted between 30th March and 29th September 2008 (six consecutive months) in the French-speaking part of Switzerland at the Centre Hospitalier Universitaire Vaudois (CHUV), five regional hospitals and one epilepsy clinic (La-Chaux-de-Fonds, Fribourg, Lavigny, Morges, Neuchâtel-Pourtalès, St-Loup). The study was approved by our ethics committee. Consecutive patients aged 16 and older presenting with SE (incident or recurrent) were included. SE was defined as an epileptic seizure of any clinical semiology, lasting for at least five minutes, or two or more seizures of shorter duration without intercurrent return to baseline clinical conditions [16]. In accordance with the vast majority of available studies, EEG was not required for diagnosis, since SE is a clinical entity [3]. However, the diagnosis of non-convulsive SE implied by definition a concomitant ictal EEG recording. Paediatric patients who have a different profile of causes and outcome [1, 17], and patients with post anoxic SE, which is often associated with a dismal prognosis [18], were excluded.

Data collection

Demographical, historical and clinical variables were prospectively collected by means of a standardised anonymous form in each participating centre by the on-site consultant neurologist or research fellow (Fribourg). At the CHUV, case assessment was performed by the staff of the epilepsy unit (four physicians). In case of unclear issues telephone contact with the participating centres was initiated. The following patient characteristics were recorded: age, gender, estimated body weight. Furthermore, we recorded location of SE onset (in-hospital vs out of hospital) and categorised extent of impairment of consciousness before treatment administration (alert, confused or somnolent, defined as arousable and interactive, vs stuporous, defined as arousable but not interactive, or comatose), clinical seizure type (simple-partial, absence, myoclonic without coma, and complex-partial, vs generalised convulsive and nonconvulsive in coma) and history of previous seizures (yes vs no). Absence SE, complex-partial SE, simple-partial SE without movements, and nonconvulsive SE on coma were defined as nonconvulsive SE. Type of previous antiepileptic treatment, SE duration before treatment institution and until seizure control, agents used, including doses, and SE aetiology were collected. Outcome at hospital discharge was categorised as return to baseline clinical condition, discharge with neurological sequelae or death.

Data analysis and statistics

After completion of all data collection, two authors (AOR, JN) consensually assessed if the pharmacological management of the index SE episode was in agreement with the most recently published Swiss guidelines [8]. The suggested protocol (drug types, dosages and sequence of administration) was considered as "standard". Benzodiazepines are recommended as the first-line treatment within 5–10 minutes (four alternatives are proposed: lorazepam 0.1 mg/kg, diazepam 0.25 mg/kg, clonazepam 0,025 mg/kg, or midazolam 0.1–0.3 mg/kg). If SE persists, phenytoin (17 mg/kg under cardiac monitoring, followed by a maintenance dose) or valproate (15–25 mg/kg, also followed by a maintenance dose) should be given, starting within 15 minutes of the SE onset (second-line). The third-line is represented by the administration of one of four anaesthetic agents: midazolam bolus 0.2 mg/kg, followed by 0.05–0.8 mg/kg/h (unclear in the original text, but taken from other recommendations [19, 20]); propofol bolus 1–2 mg/kg, then 2–10 mg/kg/h; phenobarbital bolus 5–20 mg/kg, followed by 0.5–1 mg/kg/h; or thiopental bolus 1.5 mg/kg/h, then 3–5 mg/kg/h. Standard treatment allowed inclusion of levetiracetam as a second-line regimen, even if not mentioned in the guidelines, since it is increasingly used to treat SE in patients with potential side effects to enzyme-inducing agents [11, 21, 22], using a loading dosage of at least 15 mg/kg. A previously validated clinical prognostic score (STESS) was calculated and categorised as good (<3) vs poor (≥3) [23, 24]. Aetiological classification was assessed in accordance with current guidelines [25].

A Stata software, version 9.2 for Windows, was used for statistical calculations. Normally distributed continuous variables were expressed as mean ± standard deviation; otherwise as median and range. Comparisons between the CHUV and the outside hospitals were performed with 2-sided Fisher exact tests for categorical or with the t-test or Mann-Whitney U-test, for continuous or ordinal variables, respectively. Significance was set at $P < 0.05$. No correction for multiple comparisons was applied because of the exploratory character of this study.

Results

During the study period, we recorded 54 patients treated for SE in the seven participating centres. There were no repetitive episodes. By the end of their hospitalisation, all patients had had at least one EEG recording. Thirty-six subjects were included at the CHUV and 18 in the six other hospitals (five in La Chaux-de-Fonds, three each in Lavigny, Neuchâtel and Fribourg, and two each in Morges and St-Loup). Four patients in the latter group were subsequently transferred to the CHUV, whereas one CHUV patient was initially managed in another country.

The table reports clinical data according to the site of treatment. Age, frequency of SE onset outside the hospital, prevalence of a history of previous seizures, SE severity according to the STESS score, frequency of nonconvulsive SE, prevalence of SE episodes less than 30 minutes, and total SE duration were similarly distributed among both groups. Several other items showed potentially important differences between treatment sites. However, none of these reached statistical significance. More subjects with significant impairment of consciousness, severe seizure types, SE refractory to the first two treatment lines and needing therapeutic coma induction, but also with a cryptogenic SE episode, were managed at outside hospitals. A longer latency to treatment was observed at the CHUV, where patients tended to present more often with SE arising in-hospital and with acute symptomatic aetiologies. Regarding outcome, fewer patients returned to baseline clinical conditions at the CHUV (61% vs 83%). The odds ratio for poor outcome (i.e., death or neurological sequelae at discharge) at the CHUV as compared to outside hospitals was 3.57 (95% CI: 0.8–22.1).

Treatment of most patients (91%) corresponded to the national guidelines, but less so in the peripheral hospitals as compared to the CHUV (22% vs 3%, P = 0.04). Nevertheless, nonadherence to treatment guidelines was not associated with a worse outcome (P = 0.66). Likelihood of return to baseline for patients with nonconvulsive vs convulsive SE was lower at the CHUV

Table 1

Clinical data of patients with SE treated at the CHUV and at six outside hospitals.

	CHUV	Other hospitals	P	Test †
Patients	36*	18**		
Female	22 (61%)	7 (39%)	0.154	Fisher
Age (mean, SD)	57 (19)	56 (19)	0.840	t
Onset outside hospital	32 (89%)	13 (72%)	0.142	Fisher
Known previous seizures	20 (56%)	11 (61%)	0.776	Fisher
Consciousness before treatment				
– awake, somnolent, or confused	20 (56%)	5 (28%)	0.082	Fisher
– stuporous or comatose	16 (44%)	13 (72%)		
Seizure type				
– simple- or complex-partial status	22 (61%)	7 (39%)	0.154	Fisher
– generalised convulsive or nonconvulsive status in coma	14 (39%)	11 (61%)		
– Nonconvulsive SE	15 (42%)	7 (39%)	1.000	Fisher
STESS score (median, range)	2 (0-5)	2 (0-4)	0.431	U
STESS score ≥3	15 (42%)	8 (44%)	1.000	Fisher
Duration before treatment (minutes; median, range)	105 (5 min–2years)	60 (5 min–2 weeks)	0.089	U
SE lasting <30 minutes	5 (14%)	3 (17%)	1.000	Fisher
Total duration (minutes; median, range)	135 (10 min–2.5years)	150 (10 min–90 days)	0.854	U
SE refractory to first two treatment lines	5 (14%)	7 (39%)	0.079	Fisher
Coma induction for SE treatment	2 (6%)	3 (17%)	0.319	Fisher
Treatment not in agreement with Swiss guidelines	1 (3%)	4 (22%)	0.038	Fisher
Acute symptomatic aetiology	20 (56%)	7 (39%)	0.387	Fisher
Cryptogenic aetiology	6 (17%)	6 (33%)	0.184	Fisher
Outcome				
– Returned to baseline	21 (61%)	15 (83%)	0.260	Fisher
– Survived with sequelae	10 (28%)	2 (11%)		
– Death	5 (14%)	1 (5%)		

Fisher: Fisher exact test; t: Student t-test; U: Mann-Whitney U-test; * one patient referred from abroad; ** four patients subsequently referred to the CHUV

(6/15 [40%] vs 15/21 [71%]) as compared to the outside hospitals (6/7 [86%] vs 9/11 [81%]), without reaching significance (P = 0.230, Fisher). Of the four patients referred to the CHUV from outside hospitals, only two returned to baseline conditions (one deceased, one discharged with sequelae). The patient referred to the CHUV from abroad was discharged with neurological deficits. In 8/54 patients (15%) SE lasted between 5 and 29 minutes. In these subjects, the outcomes were not different as compared to SE episodes lasting 30 minutes or longer (5/8 vs 31/46 returned to baseline, P = 1.0).

Discussion

This study confirms that the management of SE is difficult and the outcome often adverse. Indeed, one third of patients had neurological sequelae or died. The treatment received was in agreement with the national guidelines in the vast majority of instances. However, a larger proportion of treatment corresponded to national guidelines in the university centre as compared to peripheral hospitals. Furthermore, our data seem to indicate that SE patients treated in a university hospital tend to have a worse prognosis than those managed at regional centres. Finally, seizures lasting between 5 and 29 minutes account for a minority (15%) of ascertained cases.

Prognostic variability among different hospital types raises several questions regarding possible explanations. Indeed, a higher mortality in a tertiary referral centre appears counterintuitive as coverage of a university hospital typically implies a neurologist available 24/24 h, 7/7 d, and EEG availability every day, whereas in a regional or district hospital, a neurologist is on call during working hours only and EEG availability is restricted. Intensive care unit resources are also more widely available in university hospitals. Whilst the aforementioned Italian study suggested a better SE management in the rural centre, [14] this does not seem to be the case in the present study, where treatment in the university hospital was more often in agreement with guidelines. Quite surprisingly in our study, peripheral hospitals tended to have more patients with severe impairment of consciousness, generalised convulsive seizures and refractory SE episodes; factors related to a worse prognosis [4, 5, 17, 26]. Whilst age and history of previous seizures were similar among groups, acute symptomatic aetiologies and longer latency to treatment (somewhat linked to worse prognosis [4, 5, 17, 26]) showed a trend in favour of the CHUV. Cryptogenic SE, probably related to better outcome [27], was more frequent in peripheral hospitals. All these predictors very likely balanced themselves out. SE severity, estimated by the STESS score, was comparable in the two settings. Other factors must therefore account for the observed prognostic difference. The presence of comorbidities was not formally assessed in this study. These may be supposed to be more frequent in a tertiary centre, where patients with in-hospital SE tended to be more prevalent. It can also be postulated that patients tend to leave the university hospital to be referred to other centres or rehabilitation facilities earlier as compared to peripheral hospitals, thus leading to an information bias. Unfortunately, our data do not allow retrieval of hospitalisation length. Furthermore, we cannot exclude the possibility that the yield and quality of case ascertainment was critically different, as might be suggested by a higher prevalence of complex-partial and simple partial SE at the academic centre. Indeed, formal data verification by a coordinating authority was not performed, possibly generating more "generalised convulsive seizures" and "stupor/coma" in the peripheral setting, where neurological evaluations on admission and follow-up are less thorough than in the university centre.

This study produced a further important finding. Only a limited proportion of SE episodes (15%) lasted less than 29 minutes. A minimal seizure duration of 30 minutes is generally used in epidemiological surveys. However, in clinical practice, a time frame of 5 minutes has been advocated to encourage early pharmacological treatment [16]. One study found that 43% of seizures lasting between 10 and 29 minutes subsided spontaneously, whereas patients with longer seizures more often needed to be treated with an AED [28]. This ambispective study (short episodes were collected retrospectively and longer episodes prospectively) reported a higher prevalence (26%) of "short" SE episodes as compared to our survey and a clear mortality difference (19% in prolonged SE vs 3% in seizures <30 minutes, P <0.001). A larger study is needed to determine whether these differences are related to diverging study designs, different sample sizes, geographical location or chance.

Incomplete adherence to treatment guidelines, occurring in a minority of cases, was not significantly associated to SE outcome. Surprising at first glance, this observation should be reframed: SE treatment relies on relatively low evidence, [29] and prognosis is mostly influenced by aetiology [4, 5, 26, 30], age and extent of consciousness impairment represent other important predictors [4, 26, 30]. In fact, previous observations by our group focusing on the administration of "aggressive" SE treatment, i.e., pharmacological coma induction, do not suggest that a specific treatment approach correlates with a better prognosis [24].

This preliminary study is limited by its size

leading to a reduced power, by the possibility of incomplete case ascertainment in the peripheral hospitals, resulting in potential information bias, and by the lack of formally standardised outcome measures among the centres. However, it appears unlikely that recording of more simple-partial and complex-partial SE episodes in the peripheral setting would inverse the trend of prognosis difference, since these SE forms are probably less prone to result in death. Nevertheless, it is paramount to address these issues, including a thorough assessment of case severity and comorbidity in a larger prospective survey. We believe that such a study, if well-designed, may help to clarify if the prognostic difference between SE cases treated in small and large academic is real and, if so, identify the reasons and address the real impact of SE treatment guidelines in this context. The identification of modifiable features and the exact role of baseline patient characteristics and hospital settings should allow the discovery of practical ways to improve the care of patients suffering from SE.

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