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Stéphane Legriel
Bruno Mourvillier
Nicolas Bele
Jose Amaro
Pierre Fouet
Philippe Manet
François Hilpert

Outcomes in 140 critically ill patients with status epilepticus

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S. Legriel (✉) · N. Bele
Hôpital Saint-Louis, Service de Réanimation Médicale,
1 Avenue Claude Vellefaux, 75010 Paris, France
e-mail: stlegriel@invivo.edu
Tel.: +33-1-42499421
Fax: +33-1-42499426

B. Mourvillier · J. Amaro · P. Fouet · P. Manet · F. Hilpert
Hôpital Robert Ballanger, Service de réanimation polyvalente,
Boulevard Robert Ballanger, 93602 Aulnay-sous-bois cedex, France

Abstract *Objective:* Despite recent management guidelines, no recent study has evaluated outcomes in ICU patients with status epilepticus (SE). *Design and setting:* An 8-year retrospective study. *Subjects and intervention:* Observational study in 140 ICU patients with SE, including 81 (58%) with continuous SE and 59 (42%) with intermittent SE (repeated seizures without interictal recovery). *Measurements and results:* The 95 men and 45 women had a median age of 49 years (IQR 24–71). Median seizure time was 60 min (IQR 20–180), and 58 patients had seizures longer than 30 min. The SE was nonconvulsive in 16 (11%) patients and convulsive in 124 (89%), including 89 (64%) with tonic-clonic generalized seizures, 27 (19%) with partial seizures, 7 (5%) with myoclonic seizures, and 1 with tonic seizures. The most common causes of SE were cerebral insult in 53% and anticonvulsant drug withdrawal in 20% of patients. No cause was identified in 35% of patients. Median time from SE to treatment was 5 min (IQR 0–71). The SE was refractory in 35 (25%) patients. Mechanical ventilation was needed in 106 patients. Hospital mortality was 21%. By multivariate analysis, independent predictors of 30-day mortality were age (OR 1.03/year; 95% CI 1.00–1.06), GCS at scene (OR 0.84/point; 95% CI 0.72–0.98), continuous SE (OR 3.17; 95% CI 1.15–8.77), symptomatic SE (OR 4.08; 95% CI 1.49–11.10), and refractory SE (OR 2.83; 95% CI 1.06–7.54). *Conclusion:* Mortality in SE patients remains high and chiefly determined by seizure severity. Further studies are needed to evaluate the possible impact of early maximal anticonvulsant treatment on outcomes.

Keywords Cerebral insult · Electroencephalogram · Anticonvulsant therapy · Status epilepticus · ICU

Introduction

Status epilepticus (SE) is a major electro-clinical emergency associated with high mortality and morbidity rates [1]. It is defined as either continuous seizure for at least 10 min or more than two seizure episodes without full recovery of consciousness in the interval [2, 3]. Reports from the literature indicate an annual incidence of up to 41 per 100,000 population [4]. Status epilepticus may be convulsive or nonconvulsive [5]. The prognosis and treatment differ between these two presentations [2].

The management of patients with SE includes anticonvulsant medications [3], investigations for a cause, and supportive care as indicated by coma depth and organ failures; thus, patients with SE may require admission to the intensive care unit (ICU) [6]. Few studies have been specifically designed to assess outcomes in SE patients admitted to the ICU [7–9], and little is known about the management of patients with SE in the ICU.

The primary objective of this study was to identify factors associated with death in patients admitted to the ICU for SE. Our secondary objective was to identify targets for

efforts to improve the management of ICU patients with SE. To achieve these objectives, we collected data on management and outcomes via a retrospective review of 140 cases.

Patients and methods

The ethics committee of the French Society for Critical Care approved this noninterventional retrospective study. All consecutive patients admitted to the Robert Ballanger Hospital ICU with status epilepticus (SE) over an 8-year period were included. The Ballanger Hospital, a university-affiliated institution located in the Paris metropolis, has 834 beds for both medical and surgical patients, including 12 beds in a closed medical-surgical ICU. Most ICU patients are admitted through the emergency department or prehospital emergency medical system (SAMU); only 25% of patients are referred from the wards. Patients managed in the ICU for SE are discharged to the neurology department, where sophisticated equipment is available. In addition, a neurologist is available at all times for giving advice about diagnostic and therapeutic strategies in ICU patients with SE. Status epilepticus was defined as continuous seizing for at least 10 min or as more than two seizures without full recovery of consciousness in the interval [2, 3]. Intermittent SE was defined as repeated seizures, each lasting at least 10 min, with no recovery between seizures. A standardized form was used to collect the variables listed in Tables 1 and 2. Severity and organ dysfunction at ICU admission were assessed using the Simplified Acute Physiology Score II (SAPS II) [10] and the Logistic Organ Dysfunction (LOD) system score [11]. Seizure duration was determined based on data in the prehospital notes, emergency room chart, and ICU chart. We classified SE as convulsive status epilepticus (CSE) or nonconvulsive status epilepticus (NCSE) [2]. In accordance with recent definitions [5], NCSE was defined as prolonged electrographic seizure activity resulting in nonconvulsive clinical symptoms. The NCSE was categorized as electrographic SE when patients were found in a coma without significant motor seizure activity but with generalized or lateralized ictal discharges on the electroencephalogram (EEG) [5, 12].

Intermittent EEG monitoring was available for all patients upon clinician request. Mechanical ventilation was used according to standardized criteria. Patients whose Glasgow Coma Scale (GCS) score remained less than 8 despite first-line anticonvulsant therapy received endotracheal mechanical ventilation. Some patients underwent on-scene intubation because of coma subsequently shown to be related to NCSE. Finally, intubation was

Table 1 Patient characteristics and univariate predictors of ICU mortality. *OR*, odds ratio; *CI*, confidence interval; *EEG*, electroencephalogram; *SAPS*, Simplified Acute Physiology Score; *ICU*, intensive care unit; *LOD*, Logistic Organ Dysfunction score; *IQR*, interquartile range

	No. (%) or median (IQR)			OR	95% CI	Significance (p)
	All patients ($n = 140$)	Survivors ($n = 110$)	Nonsurvivors ($n = 30$)			
Demographics						
Male gender	95 (68)	74 (67)	21 (70)	1.14	0.47–2.73	0.77
Age (years)	49 (35–62)	47 (33–59)	52 (37–70)	1.03	1.01–1.06	0.01
Previous history of epilepsy	69 (49)	60 (55)	9 (30)	0.36	0.15–0.85	0.02
Seizure description						
Witnessed seizure	135 (96)	105 (96)	30 (100)	0.88	0.71–1.34	0.97
GCS at scene	6 (3–9)	6 (3–10)	3 (3–6)	0.83	0.71–0.96	0.01
Focal neurological signs at scene	54 (39)	38 (35)	16 (53)	2.16	0.95–4.90	0.06
Seizure duration (min)						
Continuous SE	60 (20–180)	60 (15–180)	75 (30–225)	1.00	1.00–1.01	0.12
Intermittent SE	2 (2–3)	2 (2–3)	3 (2.5–3)	0.94	0.56–1.57	0.82
Classification of SE						
Continuous SE	81 (58)	58 (53)	23 (77)	2.95	1.17–7.43	0.02
Intermittent SE	59 (42)	52 (47)	7 (23)			
Convulsive status epilepticus	124 (88.5)	96 (87.3)	28 (93.3)	0.49	0.10–2.28	0.36
Nonconvulsive status epilepticus	16 (11.4)	14 (12.7)	2 (6.7)			
Symptomatic SE	74 (53)	52 (47)	22 (73)	3.07	1.26–7.48	0.01
Treatments in the ICU						
SAPS II score at ICU admission	37 (24–50)	36 (24–45)	49 (29–57)	1.04	1.01–1.06	0.01
LOD score at ICU admission	7 (4–12)	6 (4–9)	17 (9–23)	1.24	1.15–1.35	< 0.0001
Time from SE to treatment (min)	5 (0–71)	3 (0–90)	15 (0–60)	0.99	0.95–1.04	0.73
Use of mechanical ventilation	106 (76)	80 (72)	26 (87)	2.43	0.78–7.57	0.12
Intermittent EEG	69 (49.3)	50 (45.4)	19 (63.3)	2.07	0.90–4.76	0.08
Refractory SE	35 (25)	23 (21)	12 (40)	2.52	1.06–5.97	0.03

Higher scores indicate a higher risk of hospital death

Table 2 Seizure classification and causes of status epilepticus. *SE*, status epilepticus; *CNS*, central nervous system; *ACD*, anticonvulsant drug

Seizure classification	All patients	Patients without previous epilepsy	Patients with previous epilepsy
Nonconvulsive SE	16 (11)	8 (50)	8 (50)
Electrographic SE	16 (100)		
Convulsive SE	124 (88.6)	63 (88.7)	61 (88.4)
Tonic–clonic generalized	89 (64)	42 (59.1)	47 (68.1)
Partial	27 (19)	16 (22.5)	11 (15.9)
Myoclonic	7 (5)	5 (7)	2 (2.9)
Tonic	1 (1)	0	1 (1.4)
Causes of SE [a]			
Alcohol-related SE	10 (7.1)	4 (5.6)	6 (8.7)
Cerebrovascular disease	24	17 (23.9)	7 (10.1)
CNS infection	(17.1)	5 (7)	1 (1.4)
Metabolic disorder	6 (4.3)	12 (16.9)	1 (1.4)
Drug poisoning	13 (9.3)	6 (8.5)	1 (1.4)
Tumor	7 (5)	3 (4.2)	0
Undetermined	3 (2.1)	24 (33.8)	25 (36.2)
ACD withdrawal	28 (20)	0	28 (40.6)

[a] Some patients had more than one diagnosis

required in some patients with aspiration pneumonia and respiratory failure or shock.

Clinical control of seizure activity and etiological management of SE were started at the first-response scene. Anticonvulsant drugs were administered according to current guidelines. Benzodiazepines (clonazepam 1 mg IV) were given either before ICU admission at the discretion of the attending physician (maximum of 3 mg) or in the ICU in patients with persistent seizure activity at ICU admission. Then, all patients received standard second-line anticonvulsant therapy (phenobarbital, 10–15 mg/kg IV; or phenytoin, 18 mg/kg IV). Refractory SE was defined as seizure activity that persisted after second-line anticonvulsant therapy and required thiopental. Thiopental was given in titrated doses until remission of the clinical and electrical seizure activity (5 mg/kg IV followed by 3–5 mg/kg h^{-1}). Patients who did not recover consciousness after first-line anticonvulsant therapy underwent electroencephalography. Patients found in electrographic SE were treated as having refractory CSE, with thiopental doses titrated to obtain a burst-suppression EEG pattern.

Computed tomography (CT) was obtained in patients with clinical evidence of trauma or focal deficits. Lumbar puncture was performed when there was a fever or clinical evidence of meningitis. Plasma anticonvulsant-drug assays and qualitative tests for toxic substances or medications associated with seizures were performed as indicated by the clinical history. Laboratory tests were obtained routinely to look for metabolic abnormalities associated with seizures, such as disturbances in serum sodium, calcium, urea, or glucose. Symptomatic SE (in contrast with idiopathic/cryptogenic SE) was defined according to 1993 guidelines and included acute symptomatic, remote symptomatic, and progressive symptomatic SE [13].

Statistical analysis

Quantitative parameters are reported as median and interquartile range (IQR 25th to 75th percentiles) and qualitative parameters such as number and percentage. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared using the Mann–Whitney U-test or the Wilcoxon test, as appropriate.

Vital status at hospital discharge was known for all study patients. Associations between patient characteristics and hospital mortality were assessed using a logistic regression model. Multivariable analysis was performed using a stepwise forward selection procedure to introduce variables whose *p*-values were smaller than 0.20 by univariate analysis. Then, the absence of a significant increase in the likelihood value after omission of each of the remaining variables was checked. Goodness of fit was evaluated by the Hosmer–Lemeshow statistic. Odds ratios (OR) and their 95% confidence intervals (CI) were computed. The *p*-values less than 0.05 were considered statistically significant. Analyses were done using the SAS 9.1 software package (SAS Institute, Cary, N.C.).

Results

Table 1 reports the characteristics of the 140 patients admitted to the ICU with SE. There were 95 men and 45 women, with a median age of 49 years (range 24–71 years). A previous history of epilepsy was noted in 69 (49%) patients.

Continuous seizures occurred in 81 (58%) patients, their median duration being 60 min (20–180). In the 59 (42%) patients with intermittent seizures, the longest seizure duration was 2 min (range 2–3 min). The NCSE

occurred in only 16 (11%) patients. Of the 124 (89%) patients with CSE, 89 (64%) had tonic-clonic generalized seizures, 27 (19%) partial seizures, 7 (5%) myoclonus, and 1 tonic seizures (Table 2). All 16 patients with NCSE had electrographic SE. The most common causes of SE (Table 2) were cerebral insult (symptomatic SE, 53%) and anticonvulsant drug withdrawal (20%). Some patients had more than one cause. No cause was detected in 35% of patients.

Time from SE onset to treatment was 5 min (range 0–71 min). The SE was refractory in 35 (25%) patients. Mechanical ventilation was needed in 106 patients, for a median duration of 2 days (range 1–7 days). All patients had neurological impairment. In addition, 30 (21%) patients had failure of one other organ, 40 (29%) of two other organs, 26 (19%) of three other organs, and 23 (16%) of four or more other organs. Median length of ICU stay was 5 days (range 2–11 days). Hospital mortality was 21% (30 deaths). In the 58 patients whose seizure time was 30 min or more, mortality was significantly increased (32.7 vs. 13.3%, $p = 0.01$).

Anticonvulsant therapy included clonazepam in all but 1 patient, phenytoin in 19 (13.6%) patients, phenobarbital in 70 (50%) patients, and thiopental in 51 (36.4%) patients. Some patients with refractory SE received, in addition to thiopental, phosphenytoin, sodium valproate, propofol, or carbamazepine.

Among the 30 patients who died, 9 died after decisions to forgo life-sustaining treatment, 6 died after nosocomial infection with septic shock, 5 had brain death, and 10 had multiple organ failure.

The results of the univariate analysis are reported in Table 1. Independent predictors of 30-day mortality were older age (OR 1.03/year; CI 1.00–1.06, $p = 0.03$), GCS at scene (OR 0.84/point; CI 0.72–0.98, $p = 0.02$), continuous seizures (OR 3.17; CI 1.15–8.77, $p = 0.03$), symptomatic SE (OR 4.08; CI 1.49–11.10, $p = 0.006$), and refractory SE (OR 2.83; CI 1.06–7.54, $p = 0.04$). When SE was defined as a seizure lasting more than 30 min, independent predictors of 30-day mortality were older age (OR 1.04/year; CI 1.01–1.07; $p = 0.03$), refractory SE (OR 4.37; CI 1.14–16.77, $p = 0.03$), and previously known epilepsy (OR 0.20; CI 0.04–0.99, $p = 0.04$).

Discussion

Although management guidelines for SE were issued recently, few data are available on the management and outcomes of critically ill patients with SE. Previous studies of ICU patients with SE were published 10–25 years ago [7–9] and none used the current operational definition of SE. We report on the management and outcomes of 140 patients who met current definitions of SE and required ICU admission. We identified several factors associated with in-hospital mortality.

The high mortality rate associated with SE (21% in our study) underlines the importance of an operational definition of SE to ensure the early diagnosis and treatment. When a seizure does not stop spontaneously, treatment for SE should be started early, for instance after 5–10 min of seizure [14], i. e., when SE is imminent as opposed to established [15]. On-scene initiation of anticonvulsant therapy appears extremely important to increase the effectiveness of first-line treatment options, which is dependent on seizure duration [16] and decreases rapidly with time to initiation [3].

The distinction between CSE and NCSE, which assists in the diagnosis of SE, also supplies prognostic information. In previous studies, mortality was 27% in patients with CSE [3] compared with 18% in those with NCSE. [17] Similarly, in our study, 20% of patients with CSE died, compared with 19% of patients with NCSE. Furthermore, our findings agree with previous results which show higher mortality rates in patients who have continuous seizures compared with intermittent seizures [4]. The mortality rate in our patients may seem low compared with those of previous studies; however, the 27% mortality rate reported by Treiman et al. may be attributable to the inclusion of patients with SE complicating cardiac arrest [3]. DeLorenzo et al. reported a 51% mortality rate but included only patients with subtle SE. In addition, 21% of their patients had SE complicating cardiac arrest [3].

Management in our study was consistent with reports on patients managed outside the ICU; thus, intravenous anticonvulsant treatment was given routinely, although early life-supporting care was also needed. Neurological failure was present in all our patients, of whom 76% required mechanical ventilation. Furthermore, 85% of patients had at least one organ failure in addition to neurological failure. The diagnostic management involved extensive investigations. The EEGs were interpreted by neurophysiologists, and neurologists assessed the patients as needed. Nevertheless, no cause was detected in 35% of patients.

We failed to clearly identify targets for further improvement. Among the five independent determinants of death, only refractory SE could have been influenced by earlier management or different treatment methods. Early in the management of a patient with SE, outcomes are dependent on age, GCS, and continuous on-scene seizure activity. The strongest predictor of death, namely refractory SE, can be identified only after treatment. The prognostic impact of refractory SE indicates a need for a specific recommendation to administer early anticonvulsant therapy tailored to the clinical and electrophysiological response.

Our study has many limitations. Firstly, a corollary of the single-center and retrospective design is uncertainty about the extent to which our population represents the full spectrum of SE patients managed in the ICU. Secondly,

our population was heterogeneous in terms of the clinical presentation and causes of SE. Because continuous EEG monitoring was not available in our ICU, neither seizure activity duration nor the proportion of patients with NCSE could be determined accurately. Thirdly, to define SE, we used the recent operational definition requiring a seizure duration of more than 10 min, instead of 30 min; however, our finding that refractory SE and continuous SE were each independently associated with survival supports the use of the more recent definition in order to encourage early intensification of anticonvulsant therapy in patients with prolonged seizures. Furthermore, predictors of death differed according to the definition used; therefore, all studies of SE must use the same seizure time to define SE. Fourthly, the fact that no cause of SE was found in 35% of our patients might suggest inadequate etiological investigations; however, we believe that our diagnostic strategy was adequate. Indeed, routine biological tests and anticonvulsant drug assays were performed in all patients, CT in 76%, and lumbar puncture in one third of patients. This work-up intensity compares favorably with the existing literature. Lastly, CSE may represent only a small proportion of all SE cases in ICU patients. Routine continuous EEG for 24–48 h has been reported to detect nonconvulsive seizures in a substantial number of comatose patients in general ICUs [18, 19].

Conclusion

In conclusion, mortality in ICU patients in SE was 21% and was predicted mainly by factors available within a few hours after ICU admission. Both the type of seizure and treatment responsiveness affected survival. Further studies are needed to compare the impact on survival of various drug combinations or of immediate maximal therapy.

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