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ORIGINAL COMMUNICATION

Status Epilepticus Severity Score (STESS)

A tool to orient early treatment strategy

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Abstract *Background* Status epilepticus (SE) treatment ranges from small benzodiazepine doses to coma induction. For some SE subgroups, it is unclear how the risk of an aggressive therapeutic approach balances with outcome improvement. We recently developed a prognostic score (Status Epilepticus Severity Score, STESS), relying on four outcome predictors (age, history of seizures, seizure type and extent of consciousness impairment), determined before treatment institution. Our aim was to assess whether the score might have a role in the treatment strategy choice. *Methods* This cohort study involved adult patients in three centers. For each patient, the STESS was calculated before primary outcome assessment: survival vs. death at discharge. Its ability to predict survival was estimated through the negative predictive value for mortality (NPV). Stratified odds ratios (OR) for mortality were calculated considering coma induction as exposure; strata were defined by the STESS level. *Results* In the observed 154 patients, the STESS had an excellent negative predictive value (0.97). A favorable STESS was highly related to survival ($P < 0.001$), and to return to baseline clinical condition in survivors ($P < 0.001$). The combined Mantel-Haenszel OR for mortality in patients stratified after coma induction and their STESS was 1.5 (95 % CI: 0.59–3.83). *Conclusion* The STESS reliably identifies SE patients who will survive. Early aggressive treatment could not be routinely warranted in patients with a favorable STESS, who will almost certainly survive their SE episode. A randomized trial using this score would be needed to confirm this hypothesis.

Key words status epilepticus · prognosis · treatment · coma induction · outcome

Introduction

Since status epilepticus (SE) is characterized by significant short-term morbidity and mortality [6, 9, 16], prompt treatment institution is recommended [17, 22, 26]. SE treatment protocols present a wide range of intensities, from small doses of benzodiazepine, to combinations of intravenously administered antiepileptic drugs, to coma induction with an appropriate anesthetic agent, such as barbiturates, propofol, or midazolam [17, 22]. Each of these therapeutic approaches bears a specific risk, and it is still not clear if the risk associated with aggressive therapy balances the potential benefit of

an improved outcome. This issue seems to be relevant especially in complex-partial SE, in which the likelihood of subsequent neurological sequelae appears lower than after generalized convulsive or non-convulsive status in coma ("subtle status") [2, 10, 13, 14, 29].

SE outcome predictors might be useful in determining treatment strategy for a given patient. In a preliminary approach, we recently developed a simple clinical prognostic score (for which we propose the name of Status Epilepticus Severity Score, or STESS), in order to predict survival, before treatment institution, of adult patients presenting with SE; it was validated on a small prospective cohort of 34 patients [20].

The main aim of this study was to assess the potential utility of the STESS in the choice of SE treatment strategy by comparing outcomes of patients with and without coma induction, stratified according to their STESS. We also analyzed whether subjects having a favorable score would additionally benefit from therapeutic coma.

Methods

Design and data collection

This was a prospective observational study carried out at three University Hospitals (Centre Hospitalier Universitaire Vaudois, CHUV, Lausanne, Switzerland; Brigham and Women's Hospital, BWH, and Massachusetts General Hospital, MGH, Boston, MA, USA). The cohort consisted of patients older than 16 years presenting during different time frames in the three participating centers: April 2006–June 2007 at CHUV, July 2004–March 2007 (with an interruption between October 2005 and May 2006, when only sporadic patients were assessed) at BWH, and December 2006–July 2007 at MGH. Apart from the transitory interruption period at BWH, subjects were recorded consecutively. The first 34 patients at BWH overlap with our previous report [20]. Clinicians in charge of the data collection at each site recorded all needed variables on patients' admission, before therapeutic interventions; they were not primarily involved in treatment choice. The STESS was calculated shortly after treatment institution (but before outcome assessment); therefore, its value did not influence the choice of treatment strategy, nor did knowledge of the outcome bias the score.

STESS description

This score relies on the assessment of age (0 or 2 points, cutoff at 65), previous history of seizures (1 point if negative, as a surrogate for acute etiology), seizure type (0, 1 or 2 points), and extent of consciousness impairment (1 point if stuporous or comatose) (Table 1); a score of 0–2 is defined as favorable, indicating low risk of death. Its rationale and preliminary validation have been previously described [20].

Definitions and variables

As in our previous work [19, 20], we defined SE as ongoing seizures, or repetitive seizures without intercurrent normalization of consciousness or return to baseline, for at least 30 minutes. This widely accepted definition for epidemiological studies allows a comparison with previous works on SE treatment. All patients had at least a routine EEG within 24 hours of admission, and follow-up recordings including EEG monitoring were performed in all patients failing to awake after clinical convulsion subsided. Subjects with SE from cerebral anoxia were excluded, owing to the almost invariably dismal prognosis related to this condition. In addition to demographic characteristics, we identified previous history of seizures, seizure semiology focusing on the worst manifestation before treatment (in descending order of gravity: nonconvulsive SE in coma, generalized convulsive, complex partial, myoclonic or absence or simple partial), time between seizure onset and institution of the first specific treatment (dichotomized as $< $ or ≥ 1 h), and SE etiology (according to ILAE criteria [1], classified as acute symptomatic, remote symptomatic, progressive symptomatic, and idiopathic/cryptogenic). As we have previously proposed [19], we also labeled etiologies as potentially fatal, if having the risk of leading to death within days-weeks unless specifically treated, even in the absence of SE. Level of consciousness before treatment was categorized as alert, somnolent (arousable and responsive) or confused, stuporous (arousable but non-responsive), and comatose (non-arousable). Outcome was assessed at hospital discharge (dead, alive but substantially impaired relative to baseline clinical condition, or returned to baseline).

Statistical analysis

Sensitivity, specificity, positive predictive value, and negative predictive value (NPV) of the STESS were estimated with their Wilson's binomial 95 % CI. Unweighted accuracy was calculated as the average of sensitivity and specificity. Chi square or Fisher exact tests were used, as needed, to compare categorical variables of interest between surviving and dead patients, and among the three centers, whereas t-tests or one-way ANOVA were applied for continuous variables. Stratified OR for mortality were estimated. Exposed patients were those with coma induction, and strata were defined by the STESS level (favorable

Table 1 Status Epilepticus Severity Score (STESS), modified after [19]. A favorable score is 0–2

	Features	STESS
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type	Simple-partial, complex-partial, absence, myoclonic*	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Total		0–6

* complicating idiopathic generalized epilepsy

vs. unfavorable). Mantel-Haenszel χ^2 tests were used to test homogeneity of OR across strata. A backward stepwise logistic regression model with mortality as dependent variable was constructed using variables with $p < 0.20$ in univariate analysis. All calculations were performed with a Stata software package, version 9.

Results

The cohort consisted of 154 adult patients (CHUV 67, BWH 61, MGH 26). Demographic and clinical features, classified by outcome, are shown in Table 2. There were 1 generalized myoclonic SE (complicationg juvenile myoclonic epilepsy), 3 absence SE, 21 simple-partial SE, 57 complex-partial SE, 53 generalized convulsive SE, and 19 non-convulsive SE with coma. The high prevalence of simple-partial and complex-partial SE probably explains the long delay before treatment in the majority of our patients. In univariate analysis, age (as a continuous variable), acute symptomatic etiology, potentially fatal etiology, absence of previous seizures, generalized convulsive or non-convulsive SE in coma, marked consciousness impairment, and coma induction were associated with higher mortality ($p < 0.05$), but gender and treatment delay were not. In the final multivariable logistic regression, age, absence of history of previous seizures, potentially fatal etiology, and seizure type were determined to be independent risk factors for mortality (Table 3). This model had an excellent goodness of fit (Hosmer-Lemshow test for 10 groups: $P = 0.73$).

Each variable was compared among the three centers: gender ($P = 0.676$, χ^2), age ($P = 0.816$, ANOVA), acute symptomatic etiology ($P = 0.489$, χ^2), potentially fatal etiology ($P = 0.133$, χ^2), history of previous seizures ($P = 0.458$, χ^2), seizure type ($P = 0.187$, χ^2), extent of consciousness impairment ($P = 0.433$, χ^2), and treatment delay ($P = 0.793$, χ^2) were not different. Although mortality ($p = 0.308$, χ^2) and STESS severity ($p = 0.793$, χ^2) were also similar, therapeutic coma was significantly less frequent at CHUV (12 %) than at the two Boston hospitals (BWH 36 %, MGH 36 %, $P = 0.004$, χ^2).

Table 4 summarizes the validity of STESS in assessing mortality risk in this multicenter cohort. The score had a very high negative predictive value for fatal outcome (0.97), with a narrow CI. A favorable STESS (0–2) was consistently related both to survival (97 % if favorable STESS vs. 61 % if unfavorable STESS, $P < 0.001$, Fisher) and likelihood to return to baseline clinical condition in surviving patients (81 % if favorable STESS vs. 35 % if unfavorable STESS, $P < 0.001$, χ^2). We also assessed the STESS performance on the subgroup of 57 patients with complex-partial SE: all 33 subjects with favorable score

Table 3 Logisitc regression model for variables associated with mortality

	OR	95 % CI	p
Age (mean ± SD)	1.03	1.00–1.06	0.045
Potentially fatal etiology [19]	4.14	1.37–12.49	0.012
History of previous seizures	0.23	0.08–0.65	0.006
Seizure type GC or NCSEC	5.80	2.11–15.90	0.001

GC generalized convulsive; *NCSEC* nonconvulsive status epilepticus in coma

Table 4 STESS characteristics related to mortality in the 154 patients. 95 % CI was calculated using a Wilson binomial distribution

	Alive	Dead	Total
Score 0–2 (favorable)	72 (97 %)	2 (3 %)	74
Score 3–6 (unfavorable)	49 (61 %)	31 (39 %)	80
Total	121 (79 %)	33 (21 %)	154

Sensitivity: 0.94 (95 % CI: 0.804–0.983)
Specificity: 0.60 (95 % CI: 0.506–0.678)
Positive predictive value: 0.39 (95 % CI: 0.288–0.497)
Negative predictive value: 0.97 (95 % CI: 0.907–0.993)
Unweighted accuracy: 0.767

Table 2 Variables of interests as compared to of mortality in the whole cohort (154 patients)

	Alive	Dead	P	Test
	121 (79 %)	33 (21 %)		
Gender (F)	62 (51 %)	15 (45 %)	0.556	χ^2
Age (mean ± SD)	57.2 ± 19.0	65.1 ± 18.3	0.035	t
Acute symptomatic etiology [1]	63 (52 %)	24 (73 %)	0.034	χ^2
Potentially fatal etiology [19]	53 (44 %)	28 (85 %)	< 0.001	χ^2
History of previous seizures	74 (61 %)	6 (18 %)	< 0.001	χ^2
Seizure type GC or NCSEC	48 (40 %)	24 (73 %)	0.001	χ^2
Consciousness before treatment				
Alert	15 (12 %)	2 (6 %)		
Somnolent/confused	47 (39 %)	5 (15 %)		
Stuporous	38 (31 %)	13 (39 %)		
Comatose	22 (18 %)	13 (39 %)	0.012	FET
Treatment after ≥ 1 h	90 (74 %)	26 (79 %)	0.603	
Coma induction for treatment	26 (21 %)	13 (39 %)	0.036	

GC generalized convulsive; *NCSEC* nonconvulsive status epilepticus in coma; *FET* Fisher's exact test

survived, whereas 7 out of 24 with a score greater than 2 died (P = 0.01, Fisher).

To investigate whether the decision to induce coma should be related to STESS, we estimated the mortality in the four groups defined by crossing the variables STESS and coma induction; the results are given in Table 5. In the group with favorable STESS, 2/63 died in the group unexposed to coma, versus 0/11 in the exposed group, while among subjects with unfavorable STESS, 35 % (18/52) died in the unexposed group compared with 46 % (13/28). The combined Mantel-Haenszel OR for mortality was 1.5 (95 % CI 0.59–3.83). The hypothesis of homogeneity of strata was not rejected by the Mantel-Haenszel test (p = 0.4). Thus, the survival was not formally found to be different depending on coma induction, regardless of the STESS score.

Discussion

The first important finding of this prospective study is that the STESS is an excellent predictor of outcome: patients with a low score have a reliably good prognosis for survival, as well as for return to baseline clinical condition (Table 4); this confirms our previous observations based on retrospective data [20]. STESS relies on proven SE predictors and is very easy to calculate in an emergency setting [20], requiring less than a minute after patient admission. Consciousness represents a critical item, which (as in our case study) should be assessed before administration of benzodiazepines (mostly by personal paramedics' reports). Inclusion of an etiology item would certainly enhance its value, but very often the SE cause can only be determined after examinations such as brain imaging and laboratory work-up (including CSF analysis), requiring a delay up to several hours or days that may prove critical for the therapeutic management. We therefore developed this score using "previous seizures" as an etiology surrogate; this information, indeed, is more likely to be available on admission. Although the score was calculated after treatment institution, the knowledge of its clinical variables may have influenced the treatment strategy; this potential bias is inherent to the observational study design. However, the fact that the observations were carried out in three different hospitals on two continents reinforces these results. The reliability of predicting survival is the most robust benefit of using the STESS: its very high NPV (the fraction of surviving patients having a favorably low score) reflects a very low rate of falsely predicted survival. Conversely, STESS does not have a good positive predictive value for death, therefore it should not be used to justify medical support withdrawal.

After adjustment for baseline state (measured with STESS), mortality was not found to be associated with coma induction (OR = 1.5 95 % CI 0.59 – 3.83). However, our study was observational, and neurologists at the different hospitals did not have a uniform treatment strategy, even if each center uses a SE therapy protocol in accordance with generally accepted guidelines [17]. Although we did not find any marked difference between our three hospitals regarding age, gender, etiology, seizure type, consciousness impairment, latency of SE treatment, and mortality (and, in general, the outcome predictors' profile reflected by the STESS) by institution, therapeutic coma frequency differed between CHUV and the two Boston hospitals, being less frequent in the former. If pharmacologic coma had a major effect on mortality, the latter would likely differ according to its changing prevalence; this was not observed among the three participating centers. Indeed, Table 5 suggests that patients suffering from SE having a favorable outcome profile on admission do not need coma, as almost all do well without it. Although, owing to the sample size, a possible slight benefit cannot be excluded (3 % mortality in the untreated group versus 0 % in the treated, non-significant), mortality is impressively low compared to that of the group with unfavorable score.

This represents, in our opinion, an important issue to be considered for the choice of SE treatment strategy. Indeed, the debate among experts focusing on whether to treat aggressively, i.e., using prompt coma induction in case of SE refractoriness, is mainly limited to patients with complex-partial SE [10, 13, 14]; conversely, there is an implicit consensus regarding subjects suffering from generalized convulsive SE [17, 22]. We showed that the STESS is also reliable in the complex-partial SE subgroup of patients, in whom potential complications arising from prolonged use of mechanical ventilation and intensive-care unit stay, such as hypotension requiring vasopressors, immunosuppression, gastroparesis, deep vein thrombosis, respiratory failure, and potentially fatal

Table 5 Mortality depending on STESS and coma induction for SE treatment

	Alive	Dead	P	Test
STESS 0–2 (favorable): 74 patients				
Coma induction –	61 (97 %)	2 (3 %)		
Coma induction +	11 (100 %)	0	1.000	Fisher
STESS 3–6 (unfavorable): 80 patients				
Coma induction –	34 (65 %)	18 (35 %)		
Coma induction +	15 (54 %)	13 (46 %)	0.301	Fisher

metabolic disturbances [4, 12, 30], might exceed the benefit of a rapid SE control. Moreover, generous use of benzodiazepines in older SE patients, leading to marked consciousness impairment, has been shown to worsen prognosis [21]. Indeed, it is debatable whether prolonged complex partial seizures in humans induce permanent structural neurological damage [2, 10, 13, 14, 29], as opposed to generalized convulsive SE forms, in which damage in the limbic structures has been confirmed both pathologically and radiologically [7, 8, 18, 23]. The fact that patients with high STESS who were treated with coma had a somewhat higher mortality than those who were not treated aggressively (Table 5) likely reflects the common policy of inducing coma especially in subjects with a more ominous prognosis, and, in our opinion, does not argue in favor of an independent deleterious effect of coma induction.

Our cohort of 154 patients, recruited prospectively on both sides of the Atlantic in three tertiary referral hospitals, is comparable to previously reported SE series in terms of demographics and mortality [6, 9, 11, 15, 16, 19]. Results of multivariable logistic regression, showing that age, etiology (for which absence of previous seizures might be viewed as a surrogate) and seizure type are independently related to mortality at hospital discharge, replicates previous findings [5, 9, 16, 19, 24, 25]. In this dataset, on the other hand, extent of consciousness impairment was not a predictor of survival, contradicting our previous findings in a retrospective adult SE series [19]. Differences in variables' assessment between prospective and retrospective designs and the likely interaction between consciousness and seizure type probably account for this discrepancy. This also suggests that, although published prospective SE series have a sample size comparable to ours [6, 9, 15] or smaller [27, 28], much larger databases should be used in order to better explore SE predictors. The consecutive recruitment experienced a transitory interruption at BWH, due to personnel shortage. We estimated that about 10 patients were missed in our database. However, this occurred independently from their clinical situation. Furthermore, this study being primarily aimed at verifying the usefulness of a score and not at estimating an incidence, we do not believe that this issue biased our results.

Another interesting issue is confirmation of the previously reported usefulness of a modified etiology categorization [19]. Indeed, in our model, "potentially fatal etiology" appears better suited to predict bad outcome as compared to the classically used "acute symptomatic" classification [1]. The latter, proposed in detail in 1993, raises problems especially regarding patients with SE following antiepileptic drug withdrawal or minor intercurrent infections, which are categorized as "acute symptomatic," but usually do not have a high mortality risk; conversely, malignant tumors may have a major impact on short-term prognosis of SE [3], yet they are officially labeled as "progressive symptomatic".

We considered mortality as primary outcome. This represents a potential limitation, since it may not only reflect the underlying clinical situation, but also the likelihood of care withdrawal that can be different among centers and cultures. Furthermore, we did not control for more subtle variables, such as the type and dose of administered agents.

In conclusion, our prospective study suggests that STESS can represent a useful tool in assessing the gravity of SE episodes and that immediate aggressive treatment, bearing inherent risks, might possibly be avoided in the majority of patients with a low score, who will almost certainly survive their SE episode, and likely return to clinical baseline. Since the observational nature of this study does not allow to formally rule out that variables that were not assessed may influence the outcome or underlie a benefit of coma induction even in patients with a favorable STESS, it would be particularly useful to confirm these observations studying patients (especially those with complex-partial SE) in a trial, using this score as an instrument to evaluate the patients at baseline.

Conflict of interest The authors declare no conflict of interest.

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