Refractory Status Epilepticus

Effect of Treatment Aggressiveness on Prognosis

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Background: Administration of antiepileptic drugs for coma induction in refractory status epilepticus (RSE) has not been widely studied. Moreover, the effect on outcome of electroencephalographic (EEG) burst suppression remains unclear.

Objective: To investigate whether various coma-inducing options are associated with different prognoses after RSE.

Design: Retrospectively assessed case series.

Setting: Two tertiary referral hospitals in Boston, Mass.

Patients: Among 127 consecutive episodes (107 patients) of status epilepticus, we identified episodes that were refractory to first-line and second-line antiepileptic drugs, needing induced coma with barbiturates, propofol, or midazolam for clinical management.

Main Outcome Measures: Short-term mortality and prevalence of return to functional baseline after the acute episode of status epilepticus were analyzed in relation to demographic and clinical variables and to treatment option (antiepileptic agents and EEG burst suppression).

Results: Forty-nine episodes of RSE (47 patients) were found, occurring more frequently in incident than in recurrent episodes of status epilepticus ($P = .06$). Mortality was 23% for patients with RSE and 8% for those without RSE ($P = .05$). Return to baseline occurred more often in the non-RSE group ($P = .04$). In 20 (61%) of 33 monitored episodes, EEG burst suppression was achieved. Demographic data, clinical variables, and outcome did not differ significantly with the various coma-inducing agents or between episodes with and without EEG burst suppression.

Conclusions: Refractory status epilepticus is more prevalent in incident than in recurrent status epilepticus and is associated with higher mortality; clinical status is less likely to return to baseline than with non-RSE. Outcome was independent of the specific coma-inducing agents used and the extent of EEG burst suppression, suggesting that the underlying cause represents its main determinant.

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REFRACTORY STATUS EPILEPTICUS (RSE) is commonly defined as status epilepticus (SE) resistant to treatment with 1 first-line antiepileptic drug (benzodiazepines) and 1 second-line antiepileptic drug (phenytoin, phenobarbital, or valproate acid).[1] Because SE tends to become more refractory to conventional treatment over time and with the number of pharmacologic agents used,[2] coma induction with an appropriate drug, such as barbiturates (BBTs), propofol, or midazolam, is advocated after failure of second-line treatment.[3] Refractory SE develops in 31% to 43% of patients with SE, with a mortality rate of at least 16% to 22%.[1,4] Despite this clinical effect, few studies have investigated RSE and its treatment. The few comparative prospective trials focusing on SE treatment assessed only first-line therapy.[5-7] Technical difficulties related to patient recruitment, problems in defining SE, and lack of consensus among neurologists at centers in the United States and Europe as to the optimal therapeutic protocol[8,9] may possibly account for the lack of relevant studies.

Most of the existing studies of RSE deal with case series of patients receiving a single coma-inducing agent,[10-13] which may not accurately reflect clinical practice, in which treatments may be combined. There is also uncertainty about the optimal extent of electroencephalographic (EEG) suppression in this setting.[14] This study investigated the effect on RSE prognosis of various coma-inducing pharmacologic options and evaluated the role of EEG burst suppression.

METHODS

DATABASE

We created a retrospective database of SE episodes in adults, confirmed by ictal or postictal (ie, focal slowing or interictal epileptiform activity) EEG, at Brigham & Women's Hospital and Massachusetts General Hospital, Boston, 2 tertiary referral centers. Their common computerized data registry was screened for the period from January 1, 1997, through March 31, 2004. The search strategy was SE, grand mal status, epilepsia partialis continua, chronic epilepsia partialis continua, or petit mal status and EEG. Status epilepticus was defined as ongoing seizures or repetitive seizures without intercurrent normalization of consciousness or return to baseline clinical values for at least 30 minutes. Of the 240 identified patients, 133 were excluded because of insufficient data (33 patients), incorrect diagnosis (ie, isolated seizures, nonepileptic seizures, or no seizures) (54 patients), age younger than 16 years (median age, 4 years; age range, 1-13 years) (33 patients), and anoxia-ischemia (13 patients).

One hundred seven patients with SE were included, accounting for 127 episodes. We conducted a prospective validation assessment, showing that this search strategy was accurate in 12 of 15 consecutive episodes of SE.

DEFINITIONS

Through manual search of discharge summaries, clinical notes, and laboratory results, we identified patients with RSE, defined as SE resistant to benzodiazepines and phenytoin, valproate, phenobarbital, or another second-line agent, who required coma induction for management of SE and in whom an endotracheal tube was inserted for treatment and not simply for airway protection. We assessed clinical and demographic variables after the earliest available description by medical or paramedical personnel. Status epilepticus was categorized as simple partial, complex partial, generalized convulsive, or nonconvulsive SE with coma; no patients with absence SE were identified. Causes of SE were categorized as acute symptomatic, remote symptomatic, progressive symptomatic, or idiopathic-cryptogenic, according to International League Against Epilepsy criteria.[15] We defined an additional etiologic category as "potentially fatal" if the underlying disease process typically leads to death if untreated. This group included acute stroke, acute central nervous system infection, severe systemic infection, malignant tumor, AIDS with central nervous system involvement, chronic renal insufficiency, systemic vasculitis, coma associated with metabolic causes, eclampsia, brain surgery, and acute cocaine intoxication.

Coma-inducing treatment was with BBTs (phenobarbital, pentobarbital), propofol, midazolam, or lidocaine hydrochloride. Outcome was classified as good if at discharge the patient's condition returned to clinical baseline; this typically corresponded to discharge to home without daily assistance. Mortality was also assessed at hospital discharge. Refractory SE control was defined as clinical and EEG cessation of ongoing seizures with no recurrence during hospitalization. Treatment failure in surviving patients was defined as coma-inducing drug administration without achievement of RSE control before change to another antiepileptic drug that eventually resulted in control of RSE. Review of EEG reports was performed for descriptions of the monitoring option (continuous or nearly continuous EEG vs intermittent, usually daily, EEG) and description of the extent of EEG burst suppression achieved, in addition to control of electrographic seizures.

Table 1. RSE vs Non-RSE: Causative and Clinical Characteristics and Outcome (All Episodes)*

Variable	Group: RSE (No. of Episodes 49)	Group: Non-RSE (No. of Episodes 78)	*P* Value
Age ≥65 y	13 (26)	25 (32)	.56
Male sex	28 (57)	34 (44)	.15
Race			
White	37 (76)	60 (77)	.99
African American	8 (16)	13 (17)	.99
Acute cause	32 (65)	46 (59)	.57
Potentially fatal cause	29 (59)	39 (50)	.36
Stupor or coma	39 (80)	52 (67)	.16
Nonconvulsive SE with coma	4 (8)	1 (1)	.07
No history of epilepsy	24 (49)	21 (27)	.01
No history of SE	42 (86)	54 (69)	.05
Hospital length of stay in surviving subjects, mean (SD) [range], d	25.3 (24.6) [4-115]	11.1 (9.71) [1-48]	<.01
Return to baseline	15 (31)	39 (50)	.04
Mortality†	11/47 (23)	5/60 (8)	.05

Abbreviations: RSE, refractory status epilepticus; SE, status epilepticus.
*Data are given as the number (percentage) unless otherwise indicated.
†Calculated for patients, not for episodes. Numerator indicates the number of patients; denominator, the total number of patients (percentage).

STATISTICAL ANALYSIS

Statistical analysis included *t* tests for continuous variables and 2-tailed Fisher exact tests for categorical variables; statistical significance cutoff was set at .05, without correction for multiple comparisons.

RESULTS

POPULATIONS AND OUTCOME

In this retrospective cohort, RSE represented 49 (39%) of 127 SE episodes and 47 (44%) of 107 patients. Refractory SE showed a clear tendency to occur more frequently in incident SE (42 [44%] of 96 episodes) than in recurrent SE (7 [23%] of 31 episodes; $P=.06$). Mortality among all patients with RSE was 11 (23%) of 47, including 10 (24%) of 42 patients with incident SE and 1 (20%) of 5 patients with recurrent SE. Return to clinical baseline after the acute episode occurred in 31% of RSE episodes vs 50% of non-RSE episodes.

Table 1 provides an overview of the analyzed historic and clinical variables for episodes of RSE vs non-RSE. Patients with RSE had a longer hospital stay ($P<.01$), less frequent history of epilepsy ($P=.01$) or SE ($P=.05$), a lower likelihood of returning to clinical baseline ($P=.04$), increased mortality ($P=.05$), and a trend toward higher prevalence of nonconvulsive SE with coma ($P=.07$). All other variables, in particular, age, cause of RSE, and extent of consciousness impairment when initially seen, did not differ.

Table 2. RSE Episodes Treated With Coma-Inducing Agents According to Outcome

Agent	No. (%) of Episodes	Alive	Dead
PRO	**10** (20)	8	2
BBTs*	**12** (24)	10	2
MDZ	**2** (4)	2	0
PRO + BBTs	**8** (16)	4	4
PRO + MDZ	**6** (12)	6	0
BBTs + MDZ	**8** (16)	5	3
PRO + BBTs + MDZ	**3** (6)	3	0
Total No. of Episodes	**49**	**38**	**11**

Abbreviations: BBTs, barbiturates; MDZ, midazolam; PRO, propofol; RSE, refractory status epilepticus.
*Two patients received lidocaine hydrochloride also; both survived.

COMA-INDUCING ANTIEPILEPTIC DRUGS AND OUTCOME

Table 2 summarizes the RSE episodes according to their coma-inducing treatment and outcome. Barbiturates (31 events) and propofol (27 events) were used more frequently than were midazolam (19 events) or lidocaine (2 events). A single coma-inducing agent was prescribed in 22 RSE episodes (45%), whereas in 27 episodes (55%) a combination of 2 (24 episodes) or 3 (3 episodes) antiepileptic drugs was used. All patients with poor outcome received either BBTs (9 events) or propofol (6 events), whereas midazolam was administered in only 3 such events. We did not find any evidence for mortality related to propofol infusion syndrome (markedly elevated creatine kinase or triglyceride levels before death).[16]

Assessment of antiepileptic comedication as first-line and second-line drugs showed that benzodiazepine plus phenytoin was by far the most frequently used option (33 of 49), followed by phenytoin plus valproate (5 of 49), benzodiazepine plus valproate (4 of 49), benzodiazepine plus phenobarbital (3 of 49), benzodiazepine alone (2 of 49), phenytoin plus phenobarbital (1 of 49), or benzodiazepine plus levetiracetam (1 of 49). Among the analyzed coma-inducing drugs, no statistically significant differences emerged for the frequency of association with the different first-line and second-line options.

Analysis of demographic, causative, and clinical variables in relation to outcome compared with administration of 1 or more coma-inducing agents is shown in **Table 3**. Monotherapy and polytherapy were not significantly different, although there was some trend for patients with no history of epilepsy to receive monotherapy.

No differences were noted among episodes in which propofol or midazolam was administered alone or in combination. However, episodes in which BBTs were used were associated with EEG burst suppression or complete suppression more frequently than episodes in which BBTs were not administered ($P=.01$). The frequency of continuous EEG monitoring was similar in all subgroups, with all percentages ranging between 58% and 71% (monotherapy, 13 of 22; polytherapy, 19 of 27; BBTs, 22 of 31; propofol treatment, 18 of 27; and midazolam treatment, 11 of 19). Episodes treated with BBTs also were associated with significantly longer hospital stay for surviving patients compared with episodes in which BBTs were not used ($P=.02$). Mortality (BBTs, 23%; propofol treatment, 24%; and midazolam treatment, 16%) and likelihood of the patient's condition returning to clinical baseline at discharge (BBTs, 26%; propofol treatment, 41%; and midazolam treatment, 21%) did not differ significantly among these 3 arms (there was a tendency in favor of propofol treatment compared with other coma-inducing drugs) $P=.12$, which was similar to other demographic, causative, and clinical variables.

Table 3. Monotherapy vs Polytherapy With Coma-Inducing Agents: Clinical, Historic Variables, and Outcome (All Episodes)*

Variable	Group: Monotherapy (No. of Episodes 22)	Group: Polytherapy (No. of Episodes 27)	*P* Value
Age ≥65 y	3 (14)	8 (30)	.30
Male sex	10 (45)	18 (67)	.16
Race			
White	18 (82)	19 (70)	.51
African American	3 (14)	5 (19)	.72
Acute cause	14 (64)	18 (67)	.99
Potentially fatal cause	13 (59)	16 (59)	.99
Stupor or coma	18 (82)	21 (78)	.99
No history of epilepsy	14 (63)	10 (37)	.09
No history of SE	19 (86)	23 (85)	.99
Monitored	15 (68)	18 (67)	.99
Burst suppression achieved	8 (36)	12 (44)	.77
Hospital length of stay in surviving subjects, mean (SD) [range], d	20.6 (22.3) [4-89]	29.5 (26.4) [4-115]	.27
Return to baseline	9 (41)	6 (22)	.21
Mortality†	4/20 (20)	7/27 (26)	.74

Abbreviation: SE, status epilepticus.
*Data are given as the number (percentage) unless otherwise indicated.
†Calculated for patients, not for episodes. Numerator indicates the number of patients; denominator, the total number of patients (percentage).

Further analysis of the treatment options listed in Table 2 disclosed that the combination of BBTs and midazolam treatment had a somewhat higher likelihood of being used in episodes related to potentially fatal cause compared with propofol alone ($P=.07$) or combined propofol plus midazolam treatment ($P=.09$). This was not reflected by the category acute symptomatic cause. In addition, time to initiation of first-line treatment was less than 1 hour in most events in which the propofol plus midazolam combination was used compared with propofol plus BBTs ($P=.03$), propofol alone ($P=.09$), and BBTs alone ($P=.11$). Also, absence of a history of epilepsy, a feature that suggests symptomatic RSE, was encountered less often in episodes treated with propofol plus midazolam combination than those treated with propofol alone ($P=.03$), BBTs alone ($P=.01$), and the BBTs plus midazolam combination ($P=.03$). Finally, achievement of burst suppression or complete suppression was observed more frequently in episodes treated with the propofol plus BBTs combination than with propofol alone ($P=.05$) or the propofol plus midazolam combination ($P=.10$) and more often in episodes treated with BBTs alone than with propofol alone

($P=.10$). Other variables, in particular, mortality, proportion of patients whose values returned to baseline clinical condition, age, SE symptoms, and consciousness impairment, did not show any major differences.

There seemed to be a higher prevalence of treatment failures (5/11 [45%]) with midazolam alone than with BBTs alone (2/15 [13%]), with propofol intermediate (5/20 [25%]), but these differences were not significant. Furthermore, no clear trend could be identified for a particular rescue antiepileptic combination: episodes in which propofol failed were successfully treated with midazolam (n=3) or BBTs (n=2), whereas episodes in which BBTs failed were rescued with lidocaine (n=1) or propofol alone (n=1) and failures with midazolam were managed with BBTs (n=3) or propofol alone (n=2).

Data on specific doses, blood levels, and treatment-induced hypotension were unavailable for most patients and were, therefore, not analyzed. Intensity of treatment was estimated by reviewing EEG effects: EEG burst suppression was seldom achieved in episodes involving failure of propofol alone (1 of 5) or midazolam alone (0 of 5) failure, as opposed to BBTs (2 of 2).

Most patients with poor outcome had clinical variables related to severe SE: potentially fatal cause in 10 of 11 patients, age 65 years or older in 8 of 11 patients, and consciousness severely impaired when initially seen in 11 of 11 patients; 6 of 11 patients received burst suppression therapy.

EEG SUPPRESSION AND OUTCOME

Achievement of burst suppression on EEG did not correlate with a better outcome: among the 33 monitored episodes, 6 of 20 achieving burst suppression and 2 of 11 not attaining burst suppression were fatal ($P=.43$), and in 5 of 20 vs 3 of 11 patients, clinical conditions returned to baseline ($P=.99$); in nonmonitored episodes, 3 of 13 patients died ($P=.99$ compared with monitored episodes) and 7 of 13 patients returned to baseline ($P=.20$ compared with monitored episodes). This negative finding was not explained by differences in prevalence of potentially fatal cause or older age. In no patient was complete, sustained EEG burst suppression achieved.

COMMENT

Refractory SE was more frequent in incident SE than in recurrent SE, but in either situation it correlated with a more aggressive underlying cause and was associated with higher mortality and a lower likelihood of return to baseline condition compared with treatment-responsive SE. The use of various coma-inducing drugs, alone or in combination, did not affect survival after RSE, nor did achievement of EEG suppression.

POPULATION

The proportion of patients with RSE in our cohort was 38% when considering all episodes and was 44% when considering only incident cases, and this is similar to the values of 31% and 43% previously described, which included recurrent episodes.[1,4] Refractory SE tended to be more frequent in incident SE episodes (44%) than in recurrent SE episodes (23%). The mortality rate with RSE in our series was 23%, similar to that in a prospective collected cohort of 10 patients treated with BBTs (20%)[12] and in 2 retrospective RSE series of 26 episodes (23%)[1] and 36 episodes (17%).[4] Whereas the first of these included only incident RSE not attributable to anoxia, the other 2 had an unclear proportion of patients with anoxic episodes and recurrent SE episodes, possibly counting the same patients more than once. Another series of patients treated with propofol showed a mortality rate of 24% after exclusion of anoxic and recurrent episodes.[13] Inasmuch as in our cohort and in another recent series[4] mortality in patients with RSE was higher than in patients without RSE, the difference in prevalence of RSE may account for much of the difference in mortality between incident and recurrent SE.

Unlike previous studies, we also assessed the proportion of patients with this clinical condition returning to baseline after the acute episode, a favorable outcome that occurred less often after RSE than non-RSE. This suggests that not only is mortality after RSE higher but also that the quality of life in survivors is probably lower than after non-RSE.

COMA-INDUCING ANTIEPILEPTIC DRUGS

Treatment of RSE was far from uniform in this cohort, inasmuch as more than 1 coma-inducing agent was prescribed in more than half of the episodes. This contrasts with previously published series in which change of medication was reported in only 2 (13%) of 16,[10] 0 of 20,[11] 6 (18%) of 33,[17] and 6 (19%) of 31 episodes.[13] We believe that our cohort more accurately reflects clinical practice than do previous reports focusing on results with use of only a single coma-inducing drug.

Among specific agents, BBTs and propofol were used more often than midazolam, and lidocaine was used too infrequently for analysis. The use of a sequence or combination of coma-inducing drugs did not differ in terms of outcome from the use of only 1 such drug. Analysis of demographic, causative, and clinical variables potentially related to mortality, which do not differ between the 2 groups (Table 3), does not support the hypothesis that the clinical approach may be determined by perceived severity of SE, in that monotherapy is assumed to be sufficient in less severe RSE episodes whereas polytherapy is necessary to treat more severe episodes. Therefore, we suggest that the underlying characteristics of each SE episode, particularly its cause,[18] determine its outcome more than the number of drugs used for its treatment.

Similar considerations apply to the choice of specific third-line drugs; episodes in which treatment with propofol and midazolam were used showed no significant differences compared with episodes in which these drugs were not prescribed. In contrast, BBTs tend to be associated with a higher likelihood of achieving burst suppression on EEG and a significantly longer hospital stay, but the outcome was similar to that with the other agents. Whereas hospital stay is likely a direct consequence of the longer half-life of BBTs compared with propofol and midazolam,[19] the higher prevalence of burst suppression may reflect that BBTs, alone or in combination, were preferred in SE episodes with more severe clinical fea-

tures and were therefore applied more aggressively, as suggested by a recent meta-analysis.[20] Of the 17 episodes in which BBTs were used and led to EEG burst suppression, 11 patients had high therapeutic or supratherapeutic blood levels (1 had a low level and in 5 patients blood levels were not checked). The blood levels of those treated with propofol or midazolam were not assessed. Analysis of the pharmacologic combinations used for coma induction corroborates this impression; the combination propofol plus midazolam seemed to be used in less severe episodes than did BBTs plus midazolam and, to a lesser extent, BBTs alone and propofol alone. Use of BBTs plus midazolam did not correlate with achievement of EEG burst suppression, as opposed to BBTs alone or BBTs plus propofol.

No difference in outcome was found among different coma-inducing options. Similarly, the cited meta-analysis[20] suggested that, although BBTs were more effective than treatment with midazolam or propofol in controlling RSE, they were not associated with decreased mortality.[20] Treatment failure in patients ultimately surviving was equally distributed among the 3 major treatment options, and failure of a particular treatment did not imply that one specific drug would be better than another as subsequent rescue treatment.

EEG BURST SUPPRESSION

A further interesting point is the lack of correlation of EEG burst suppression with outcome, especially inasmuch as in our series this goal was not specifically applied to more severe RSE episodes, allowing a comparison between the 2 groups (ie, episodes achieving or not achieving burst suppression). A previous retrospective study found mortality in 35 BBT-treated episodes to be 0% after simple electrographic seizure control, 75% after burst suppression, and 40% after complete suppression.[14] The low prevalence of EEG burst suppression in this study (41%), compared with 38%[17] to 60%[11] (the latter including complete suppression) in other series, does not reflect a higher mortality rate. Indeed, mortality seems lower than in other studies selectively analyzing the same coma-inducing drug (midazolam, 17%-61%; propofol, 57%-88%; and BBTs, 20%-50%[10-12,17]), although different patient selection, in particular, inclusion of those with anoxic episodes, may account for these discrepancies. These data support the hypothesis that it is not the type or aggressiveness of the treatment but the underlying cause of RSE that determines outcome. The lack of demonstrated advantage of treatment to burst suppression may argue against the routine administration of such aggressive treatment, especially since in 1 series generous use of benzodiazepines was reported to correlate with a poor outcome in critically ill elderly patients.[21]

The main limitation of this study is its retrospective design. However, to our knowledge, this is the largest RSE series to date and provides no evidence of differences in RSE outcome, for either mortality or return to baseline clinical condition, between monotherapy and polytherapy with coma-inducing agents or among specific coma-inducing agents. Furthermore, achievement of burst suppression at EEG did not influence prognosis. A well-designed prospective clinical trial is needed to confirm these findings.

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Additional Information: Available online at http://www.archneurol.com are video 1 (patient before starting betamethasone treatment) (note the evident disturbance of stance and gait, and impaired control of the head, neck, and skilled movements) and video 2 (patient after 4 weeks of betamethasone treatment) (note that the disturbance of stance and gait has been clearly reduced, and there is increased control of the head, neck, and skilled movements, as evidenced in his ability to go up and down the stairs. In addition, note the increased body weight and the moon face.).

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Correction

Clarification. In the Original Contribution titled "Refractory Status Epilepticus: Effect of Treatment Aggressiveness on Prognosis" by Rossetti et al published in the November issue of the ARCHIVES (2005;62:1698-1702), on page 1701, left-hand column, the last sentence of the "EEG Suppression and Outcome" subsection of the "Results" section should have read as follows: "No patient achieved complete, sustained EEG suppression."