Predictors of Outcome in Refractory Status Epilepticus

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Objective: To further characterize the demographics, outcomes, and prognostic factors for refractory status epilepticus (RSE).

Design: Retrospective analysis of all the episodes of RSE treated between January 1, 1999, and August 30, 2011.

Setting: Neurointensive care unit within a tertiary referral center, Mayo Clinic, Rochester, Minnesota.

Patients: Refractory status epilepticus was defined as generalized convulsive or nonconvulsive status epilepticus (SE) that continued despite initial first- and second-line therapies. Exclusion criteria were aged younger than 18 years, anoxic/myoclonic SE, psychogenic SE, simple partial SE, and absence SE.

Main Outcome Measures: Functional outcome was defined by modified Rankin scale (mRS) dichotomized into good (mRS, 0-3) and poor (mRS, 4-6). Functional decline was defined as a change in mRS greater than 1 from hospital admission to discharge.

Results: We identified 63 consecutive episodes of non-anoxic RSE in 54 patients. Anesthetic agents were used in 55 episodes (87.30%), and duration of drug-induced coma was (mean [SD]) 11.0 (17.9) days. In-hospital mortality was 31.75% (20 of 63 episodes). Poor functional outcome at discharge occurred in 48 of 63 episodes (76.19%). Hospital length of stay was (mean [SD]) 27.7 (37.3) days. Duration of drug-induced coma ($P = .03$), arrhythmias requiring intervention ($P = .01$), and pneumonia ($P = .01$) were associated with poor functional outcome. Prolonged mechanical ventilation was associated with mortality ($P = .04$). Seizure control without suppression-burst or isoelectric electroencephalogram predicted good functional recovery ($P = .01$). Age, history of epilepsy, previous SE, type of SE, and anesthetic drug used were not associated with functional outcome.

Conclusions: Three-quarters of patients with RSE have a poor outcome. Achieving control of the SE without requiring prolonged drug-induced coma or severe electroencephalographic suppression portends better prognosis.


REFRACTORY STATUS EPILEPTICUS (RSE) has been defined variably in the literature as seizures that do not respond to 21–4 or 3–6 different antiepileptic medications, usually intravenous benzodiazepines as a first-line agent and intravenous phenytoin, phenobarbital, or valproic acid as a second-line agent. Alternatively, RSE has been defined by the duration of seizure activity of 1 or 2 hours. Thus, no universally accepted definition of RSE exists. A subdefinition has been proposed for superrefractory SE encompassing those with SE that continues or recurs 24 hours or longer after the onset of anesthetic therapy, including cases in which SE recurs on reduction or withdrawal of anesthesia.

With the inherent limitations of these varying definitions, RSE occurs in 9% to 44% of SE cases. Series have reported mortality rates ranging from 12% to 77%, with a meta-analysis of 193 patients between 1980 and 2001 reporting a mortality rate of 48%. Series from 2002 to the present report a slightly lower, but significant, mortality rate ranging from 11.1% to 39.0%.

Risk factors for RSE include new-onset seizures, focal motor seizures, and acute central nervous system disorders, such as encephalitis. Single series and a meta-analysis of patients with RSE have shown an association of mortality with older age, etiology, and seizure duration.

The optimal management of RSE remains unclear. Because SE becomes more resistant to conventional antiepileptic drugs (AEDs) over time, early suppres-
sion through induction of coma (midazolam, propofol, or barbiturates), such as thiopental in Europe or pentobarbital in the United States, is recommended. Pharmacological management of RSE has only been studied in small retrospective reviews and prospective studies without controls. Various anesthetic agents are used, most commonly midazolam, propofol, or barbiturates. In practice, multiple anesthetic agents can be used sequentially or in combination. Data from head-to-head comparisons between single agents is limited.

Refractory status epilepticus—particularly when ongoing for months—concerns physicians and families, and questions regarding functional outcome quickly arise. The objective of this study was to evaluate the outcome and to identify prognostic factors for RSE.

METHODS

This study was a retrospective analysis of all consecutive adult patients treated for RSE at St Mary’s Hospital, Rochester, Minnesota, between January 1, 1999, and August 30, 2011. Cases were identified and clinical data acquired through queries of the computerized electroencephalographic (EEG) report system and the medical record system.

Inclusion criteria included the following: (1) patient aged 18 years or older, (2) RSE defined as generalized convulsive status epilepticus (GCSE) or nonconvulsive status epilepticus (NCSE) (partial or generalized onset) unresponsive to treatment with 2 AEDs and/or requiring anesthetic agents for seizure control, and (3) continuous EEG monitoring. Exclusion criteria were (1) anoxic/myoclonic SE, (2) psychogenic SE, (3) simple partial SE, and (4) absence SE. Patients were further classified as being superrefractory if seizures continued or recurred 24 hours or longer after the onset of anesthetic therapy, including cases in which SE recurred on reduction or withdrawal of anesthesia.

Neither history of epilepsy, repeat SE, or type of SE predicted mortality or functional outcome. Fourteen of 54 patients were considered low risk based on clinical characteristics on presentation. We compared mortality and functional outcome among low- and high-risk patients and found no significant differences between the groups.

Neither serum glucose, lactate, or white blood cell (WBC) count correlated with outcome. Mean (SD) cerebrospinal fluid (CSF) protein concentration was 65.1 (53.48) mg/dL (to convert to grams per liter, multiply by 0.001); higher protein was associated with poor functional outcome (P = .03). Mean (SD) CSF WBC count was 12.5 (26.2) ×10^3/μL (to convert to ×10^6/L, multiply by 0.001); higher CSF WBC count was associated with poor functional outcome (P = .03). Paraneoplastic antibodies were analyzed from CSF in 14 episodes, of which 3 were abnormal, and included the following: (1) N-methyl-D-aspartate (NMDA) receptor antibody, (2) NMDA and voltage-gated potassium channel antibodies, and (3) antineuronal nuclear antibody 1 in a patient with metastatic spindle cell carcinoma.

TREATMENT

The first- and second-line drugs of choice were most commonly lorzepam (60%) and fosphenytoin sodium (52%), respectively. The most commonly used anesthetic agent on clinical characteristics on presentation. Those younger than 54 years who had a history of epilepsy and admission APACHE II (Acute Physiology and Chronic Health Evaluation II) scores lower than 23 were defined as low risk.

Descriptive summaries were reported as mean (SD) or median and range for continuous variables and frequencies and percentages for categorical variables. Categorical outcomes of interest were compared using the χ² test or Fisher exact test. The Wilcoxon rank sum test was used to compare continuous outcomes of interest. All the tests were 2 sided; P < .05 was considered statistically significant. Statistical analyses were performed using SAS, version 9.2, software (SAS Institute, Inc). This study was approved by the Mayo Clinic Institutional Review Board.
was midazolam (n = 38), followed by propofol (n = 33), pentobarbital (n = 16), isoflurane (n = 3), ketamine (n = 3), and lidocaine (n = 1). Figure 2 shows the number of antiepileptic and anesthetic drugs required to control seizures in our cohort. One patient underwent surgery and another electroconvulsive therapy; both were ineffective. The anesthetic drugs used did not correlate with outcome. The requirement for anesthetic drugs over the cohort mean of 11 days was associated with poor functional outcome ($P = .01$) (Figure 3). Analysis using the receiver operating characteristic curve approach confirmed a similar cut-off of 10 days ($P = .01$). To account for possible changes in treatment over time, we compared mortality and functional outcome during the first and second halves of the study period and found no significant differences between the 2 periods.

**SYSTEMIC COMPLICATIONS**

Cardiac arrhythmias occurred in 21 of 60 episodes (35.00%) and required intervention in 14 of 21 cases (66.67%); the need for intervention correlated with poor functional outcome ($P = .01$). One patient experienced a non-ST-segment elevation myocardial infarction. Pulmonary edema was present in 21 of 58 episodes (36.21%). Hypotension and hypoxia were common, occurring in 45 of 57 episodes (78.95%) and 20 of 56 episodes (35.71%), respectively. Neither the presence of hypotension nor hypoxia was associated with outcome. Pneumonia occurred in 39 of 56 cases (69.64%) and was diagnosed at a mean of 5 days after hospital admission. The presence of pneumonia predicted a poor functional outcome ($P = .01$). Mechanical ventilation was required in 57 of 63 episodes (90.47%), of which 20 required tracheostomy. Longer duration of mechanical ventilation was associated with in-hospital death ($P = .04$). Acid-base disturbances were present in 40 of 56 episodes (71.43%). The most common acid-base disturbance was respiratory alkalosis (n = 19, 33.93%), followed by respiratory acidosis (n = 14, 25.00%); neither correlated with outcome.

**EEG SUPPRESSION**

Isoelectric suppression was reached in 4 cases; 2 patients died and 2 patients had an mRS score of 5 at discharge, improving to mRS 1 and 4 at 9- to 12-month follow-up. Suppression burst was reached in 27 cases, 22 cases (81.48%) of which had poor functional outcome. Of these, 8 patients died and 4 patients did not have post-discharge follow-up data available. Of the remaining 10, the conditions of 6 patients worsened, 3 improved, and 1 was unchanged at follow-up. Seizure control without SB or isoelectric EEG was documented in 16 episodes and correlated with a good functional outcome at hospital discharge ($P = .01$). Of the 8 cases with good functional outcome at discharge, 4 patients had no subsequent fol-
low-up data, the condition of 1 patient worsened, the condition of 1 patient improved further, and the conditions of 2 patients remained stable. In 16 episodes, the level of EEG suppression was not clearly documented. The level of EEG suppression was not associated with number of days on anesthetic agents.

OUTCOME

Transition to palliative care preceded death in 16 of 20 cases (80.00%). Other causes of death were brain death due to diffuse cerebral edema, propofol infusion syndrome (2 patients), and severe pneumonia. Premorbid functional status and outcome at hospital discharge were available for 62 episodes. Functional decline occurred in 37 episodes; premorbid functional status was preserved in 8 episodes. Prolonged hospital length of stay was associated with poor functional outcome \((P = .04)\). Among survivors, follow-up data were available in 32 of 43 episodes (74.42%); the conditions of 13 patients improved, the conditions of 13 patients declined, and the condition of 6 patients did not change. Of the 13 patients who improved, 9 changed from poor to good functional outcome. Of the 13 patients that declined, 2 changed from good to poor functional outcome. At least 1 poor prognosticator was present at discharge in 7 of 9 cases with poor functional outcome who later improved to an mRS score of less than 3. Of 6 patients with RSE lasting longer than 1 month, 4 patients survived with a mRS score of 5 at hospital discharge. In the 3 patients for whom follow-up data were available, the mRS scores at 9 to 12 months were 1, 3, and 4. Detailed information for each episode is available in the eTable.

CLINICAL CHARACTERISTICS

While functional decline tended to be more frequent in older patients, age was not associated with mortality in our cohort. Age has been associated with a higher mortality in nonrefractory SE\(^{29,30}\) as well as in RSE in a meta-analysis of 193 patients\(^23\); however, this association was not seen in a smaller single-center series.\(^15\) In most of our patients, mortality was determined by withdrawal of life-support measures after failure to stop drug-induced coma without return of seizures rather than by systemic complications, which would be the factors expected to provoke higher mortality in older patients.

A history of epilepsy was common in our series. A similar high incidence of preexisting epilepsy had been reported by Rossetti et al.\(^14\) History of epilepsy, previous SE, or type of SE did not influence the outcome. This is in contrast to the findings of a recent series by Power et al\(^31\) that found that patients with no prior epilepsy needed longer
anesthetic time and had poorer outcomes than patients with known epilepsy. However, only 5 of 27 episodes were not preceded by a diagnosis of epilepsy in that cohort, making it difficult to draw a conclusion about the significance of this finding. We did not expect the type of SE to influence outcome because almost all our cases were nonconvulsive by the time treatment was initiated.

Both higher CSF protein and higher CSF WBC count were associated with poor functional outcome. These findings may simply reflect increased inflammation and represent a marker of the severity of brain disease. A much larger cohort would be necessary to understand the prognostic value of these variables in RSE from specific causes.

**TREATMENT AND COMPLICATIONS**

Choice of AED and order of their initiation after the initial first- and second-line agents were highly variable in our cohort, which reflects clinical practice. Among anesthetic agents, midazolam and propofol were more commonly used than pentobarbital. Isoflurane, ketamine, and lidocaine were used too infrequently for analysis. Our results support existing data suggesting that choice of anesthetic agent does not strongly influence outcome. Prolonged requirement for anesthetic coma was strongly associated with poor functional outcome and with functional decline.

Mechanical ventilation was required in more than 90% of cases, one-third of which ultimately required tracheostomy. Longer duration of mechanical ventilation was associated with mortality. Cardiac arrhythmias requiring intervention and pneumonia predicted poor functional outcome. Pneumonia occurred more frequently than in other series, probably due to the refractory nature of our cohort. Hypotension was the most common complication but did not influence outcome, which is consistent with the findings of a previous meta-analysis.

Because changes in practice might have occurred over time, we compared mortality and functional outcome in the first and second halves of our study period. The outcomes did not differ between these 2 intervals.

**EEG SUPPRESSION**

Seizure control without SB or isoelectric EEG was associated with a good functional outcome in our cohort while 85% of episodes in which SB and 100% of episodes in which isoelectric suppression was reached had poor functional outcomes. While absolute conclusions cannot be offered with only 4 episodes reaching isoelectric suppression, the trend is clear: prognosis is poorer when pronounced suppression is necessary to control the seizures. Patients in SB still have seizures and having to achieve isoelectric background to control seizures is most likely reflective of more severe and refractory brain disease. Alternatively, our findings could suggest that deeper levels of EEG suppression lead to poorer outcomes due to detrimental effects of prolonged anesthesia. This is not a likely explanation as only 3 deaths in our series could directly be linked to complications of anesthesia (2 with propofol infusion syndrome and 1 with pneumonia). Our findings differ from previously published data, which suggested no association of EEG suppression with outcome.

**OUTCOME**

The in-hospital mortality rate in our series was similar to mortality rates reported in recent series. When taken as a whole, functional outcomes were poor. However, as we reported in a previous study restricted to patients with RSE lasting more than 1 week, some patients can recover over time. In our cohort, 2 patients ultimately reached good functional outcomes even after more than 1 month in anesthetic coma. Others have also reported patients with satisfactory recovery after RSE lasting weeks or months. Therefore, we think that patients with RSE should be treated aggressively and treatment options should be exhausted before palliative care is discussed with families.

**STRENGTHS AND LIMITATIONS**

Our case analysis has some limitations. Conclusions may be tentative because our patients were extremely sick, requiring intensive care unit admission, longer duration of anesthetic coma, and longer hospital stay than in other studies of RSE, and thus may not be applicable to all the cases of SE failing 2 AEDs. There was variation in treatment among subjects as is expected for a retrospective study. We could not determine the exact duration of SE prior to treatment initiation, an often difficult task even when first evaluating some of these patients in the emergency department. Although ours is one of the largest series of truly RSE presented to date, our analysis may have been underpowered to detect some associations. Our study included multiple comparisons, thereby creating the potential for inherent errors; however, the correlations seem biologically plausible. To ensure that multiple sampling error did not alter the validity of our associations, we duplicated the analysis after removing all repeat episodes of RSE and found no differences in the associations.

Causes of RSE in our cohort were too diverse to allow for analysis of the impact of discrete causative categories on functional outcome. We also lacked follow-up data in a minority of our survivors; half of these cases were discharged with poor functional outcome but might have improved over time.

Our investigation comprises a large sample size for a single-center study of a fairly rare condition and the use of continuous EEG monitoring documenting persistent SE in all the cases. During the period of study, neurointensivists directed the care of the patients, thus creating homogeneity of practice. More than half of our patients required more than 1 anesthetic agent, which accurately reflects clinical practice when treating refractory cases of SE. This is in contrast to findings in multiple series of RSE in which only 1 anesthetic agent was used.

We conclude that mortality is high in RSE and is independent of choice of anesthetic agent, type of SE, and pre-existing epilepsy. Cardiopulmonary complications are common and increase the risk of mortality and poor functional recovery, but outcome is primarily dependent on
the success or failure of aborting the seizures. Once non-anoxic SE becomes refractory, the clinical course and outcome of the patient are determined by the severity of the SE. Aggressive EEG suppression does not appear to improve outcomes in RSE, and prognosis becomes more unfavorable the longer patients remain in a drug-induced coma. Yet, some patients can regain function even after prolonged RSE.

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Online-Only Material: The eMethods and eTable are available at http://www.jama.neuro.com.

REFERENCES