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Good Outcome in Cardiac Arrest Patients in Refractory Status Epilepticus: A Result of Aggressive Treatment or EEG Reclassification

Neurologic outcome of postanoxic refractory status epilepticus after aggressive treatment.

Beretta S, Coppo A, Bianchi E, et al. *Neurology*. 2018;91(23):e2153-e2162. doi:10.1212/WNL.0000000000006615. Epub October 31, 2018.

Objective: To investigate neurologic outcome of patients with cardiac arrest with refractory status epilepticus (RSE) treated with a standardized aggressive protocol with antiepileptic drugs and anesthetics compared to patients with other electroencephalogram (EEG) patterns. Methods: In the prospective cohort study, 166 consecutive patients with cardiac arrest in coma were stratified according to 4 independent EEG patterns (benign, RSE, generalized periodic discharges [GPDs], malignant nonepileptiform) and multimodal prognostic indicators. Primary outcomes were survival and cerebral performance category (CPC) at 6 months. Results: The RSE occurred in 36 (21.7%) patients and was treated with an aggressive standardized protocol as long as multimodal prognostic indicators were not unfavorable. The RSE started 3 $\pm$ 2.3 days after cardiac arrest and lasted 4.7 $\pm$ 4.3 days. A benign EEG pattern was recorded in 76 (45.8%) patients, a periodic pattern (GPDs) was seen in 13 (7.8%) patients, and a malignant nonepileptiform EEG pattern was recorded in 41 (24.7%) patients. The 4 EEG patterns were highly associated with different prognostic indicators (low-flow time, clinical motor seizures, N20 responses, neuron-specific enolase, neuroimaging). Survival and good neurologic outcome (CPC 1 or 2) at 6 months were 72.4% and 71.1% for benign EEG pattern, 54.3% and 44.4% for RSE, 15.4% and 0% for GPDs, and 2.4% and 0% for malignant nonepileptiform EEG pattern, respectively. Conclusions: Aggressive and prolonged treatment of RSE may be justified in patients with cardiac arrest with favorable multimodal prognostic indicators.

Commentary

Targeted temperature management (TTM) with mild hypothermia markedly improved outcome of comatose patients after cardiac arrest in several large trials, but presently, there are no other interventions that have demonstrated efficacy in this patient population. Prognostication for a sizable number of patients remains difficult despite multiple tests that are typically utilized. Withdrawal of life-sustaining treatment remains the leading proximal cause of death in patients who have poor outcome.

Prior to the advent of TTM, status epilepticus was considered to represent irreversible brain injury, with virtually no hope for meaningful recovery.[1] This, of course, is no longer true in the TTM era, when a small number of survivors were initially reported[2] and subsequently investigated in other studies. Nonetheless, the presence of status epilepticus typically portends dismal prognosis, while electroencephalogram (EEG) features such as background continuity and reactivity positively correlate with survival.[2]

It should then be of great interest that Beretta et al report their cohort of 166 consecutive patients with cardiac arrest in coma: 54.3% of patients with refractory status epilepticus (RSE) survived and 44.4% had good long-term outcome. Patients with status epilepticus were treated with anesthetic-induced coma if necessary. They conclude that aggressive and prolonged treatment of RSE may be justified in patients who have other favorable markers suggestive of good outcome, and the implication is that the good outcome was a result of this treatment. This is a remarkable achievement, particularly since about half of them underwent extracorporeal membrane oxygenation. As the authors note, the rate of good outcome is several fold higher than what other major papers had reported, which is typically less than 10%. As a reference, the survival rate is approximately 75% from all causes of nonanoxic RSE.[3] Of note, this study was done using a limited 4-channel continuous EEG, with full recordings performed twice or more as needed. Whether full continuous EEG recording is needed or

not in this arena remains unclear, but in my opinion, the setup is sufficient for this study.

These results do need to be interpreted in the proper context, as reading just the title and abstract in this case can be misleading. Firstly, the total proportions of patients who survived (77/166 = 46%) or had good long-term outcome (70/166 = 42%) in this cohort do not differ significantly from other studies in terms of survival or long-term outcome. The proportion of patients with RSE (21.7% of the cohort) is more or less in line with the 10% to 35%[4] seen in other studies, though most report status epilepticus rather than RSE.

Aside from aggressive treatment of status epilepticus, what might lead to this marked discrepancy in outcome? One possibility is that this could be due to the nature of the EEG characterization utilized by the authors. This study categorizes the EEGs into 4 classes: (1) benign (continuous and/or reactive), (2) RSE without any generalized periodic discharges (GPDs) < 2.5 Hz, (3) GPDs < 2.5 Hz, and (4) malignant nonepileptiform patterns (discontinuous and unreactive, an essentially catastrophic group). The definition of status epilepticus itself originated from the Salzburg criteria, but the authors have chosen not to implement the portion of the definition that allows patients with epileptiform discharges <2.5 Hz with motor phenomena to be categorized as status epilepticus.[5] As such, status myoclonus at <2.5 Hz is not included in the RSE category and only 18.7% of patients with RSE were in status myoclonus. This is a far lower number than previously reported in other groups, ranging up to 70% to 89%.[2,6] It is very likely that applying another definition of status epilepticus would have resulted in a different patient cohort in the RSE grouping.

In addition, another surprising finding of the current paper is that patients in the GPD group had extremely poor outcome, rivaling the malignant nonepileptiform patterns group, with essentially nobody having good long-term outcome. This is in contrast to another study of GPDs, which reports up to 22% with good outcome, typically associated with good background activity.[7] Again, it is possible that the 2 studies examined a significantly different set of patients.

Are there any benefits in classifying the EEGs in the fashion utilized by the investigators? Certainly, an argument can be made that many patients in the RSE group probably should have been a subset of the "Benign EEG pattern" group—and of course that group would have a high percentage good outcome, whether they experienced status epilepticus or not. Recent studies have emphasized the importance of the specific EEG patterns in determining the outcome of myoclonic status epilepticus, for example.[8] It would have been helpful to know how many of these RSE patients would have been classified in the benign EEG versus GPD versus malignant EEG patterns, had RSE not been taken account. On the other hand, this classification facilitates identification of a target population for aggressive seizure management while minimizing futile treatments. Furthermore, there are no universally accepted methods of categorizing EEGs in these patients, though some have been proposed.

Overall, it does appear that the outcome measures in this study may not be particularly valid comparators to previously published studies. Taking these caveats into account, good outcomes in this study still appear to be higher than expected. One previous study had failed to demonstrate improved outcome with generally moderate, unstandardized treatment of electrographic status epilepticus in this population.[9] It is quite likely that standardized, aggressive treatment in a carefully selected patient cohort has had some benefit.

Nevertheless, it is important to emphasize that it cannot be concluded that the good outcome in patients in RSE reported in this study is the result of aggressive status epilepticus treatment. For this, we will have to wait for the results of the highly anticipated Treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation (TELSTAR) trial[10] which randomizes patients with postcardiac arrest electrographic status epilepticus to suppression of electrographic seizures versus no treatment. It is noteworthy that the TELSTAR definition of status epilepticus differs from this study and is more likely to reflect a more typically described postarrest status epilepticus population. As a result, it is not clear whether the trial results, whether positive or negative, will be generalizable to the proposed classification system in this paper. In the interim, regardless of whether classification system is sound or whether their outcome measures are valid comparators to previous studies, the rational principles from this study in the care of this patient population should be appreciated: identification of patients with a chance of good outcome and aggressively treating RSE while deescalating futile aggressive treatment in patients with likely poor outcome.

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