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A Cry for Survival? Rhythmic and Periodic EEG Discharges as Treatment Targets Following Cardiac Arrest

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Treating Rhythmic and Periodic EEG Patterns in Comatose Survivors of Cardiac Arrest

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Background: Whether the treatment of rhythmic and periodic electroencephalographic (EEG) patterns in comatose survivors of cardiac arrest improves outcomes is uncertain. Methods: We conducted an open-label trial of suppressing rhythmic and periodic EEG patterns detected on continuous EEG monitoring in comatose survivors of cardiac arrest. Patients were randomly assigned in a 1:1 ratio to a stepwise strategy of antiseizure medications to suppress this activity for at least 48 consecutive hours plus standard care (antiseizure-treatment group) or to standard care alone (control group); standard care included targeted temperature management in both groups. The primary outcome was neurologic outcome according to the score on the Cerebral Performance Category (CPC) scale at 3 months, dichotomized as a good outcome (CPC score indicating no, mild, or moderate disability) or a poor outcome (CPC score indicating severe disability, coma, or death). Secondary outcomes were mortality, length of stay in the intensive care unit (ICU), and duration of mechanical ventilation. Results: We enrolled 172 patients, with 88 assigned to the antiseizure-treatment group and 84 to the control group. Rhythmic or periodic EEG activity was detected a median of 35 hours after cardiac arrest; 98 of 157 patients (62%) with available data had myoclonus. Complete suppression of rhythmic and periodic EEG activity for 48 consecutive hours occurred in 49 of 88 patients (56%) in the antiseizure-treatment group and in 2 of 83 patients (2%) in the control group. At 3 months, 79 of 88 patients (90%) in the antiseizure-treatment group and 77 of 84 patients (92%) in the control group had a poor outcome (difference, 2 percentage points; 95% confidence interval, −7 to 11; P = 0.68). Mortality at 3 months was 80% in the antiseizure-treatment group and 82% in the control group. The mean length of stay in the ICU and mean duration of mechanical ventilation were slightly longer in the antiseizure-treatment group than in the control group. Conclusions: In comatose survivors of cardiac arrest, the incidence of a poor neurologic outcome at 3 months did not differ significantly between a strategy of suppressing rhythmic and periodic EEG activity with the use of antiseizure medication for at least 48 hours plus standard care and standard care alone.

Commentary

The emergence of rhythmic and periodic electroencephalographic (EEG) patterns in some survivors of cardiac arrest is both a mystery and a potential opportunity for treatment. Why such patterns emerge after hypoxia or ischemia is not clear, although it has been suggested that widespread synaptic failure leading to disinhibition of excitatory pyramidal cells might lead to the propagation of generalized periodic discharges (GPDs).[1] The pathophysiology of lateralized periodic discharges is similarly unclear, although many theories have been proposed.[2]

The following statements can be made despite the uncertainty. First, rhythmic and periodic EEG patterns seen after cardiac arrest are a reflection of brain injury. Second, discharging neurons must be alive at the time their discharges are

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being recorded. Third, the firing of discharges must have some metabolic cost.

We can therefore suppose that the discharges are an acute pathological reaction to injury (in some casesa form of status epilepticus), whose ongoing metabolic cost risks causing further harm to the tissues producing them. The discharges may be the death cry of irreversibly damaged neurons, but as known from other pathologies, such discharges can be observed in reversible processes.[3] Perhaps, by intervening early to reduce or stop the discharges, some proportion of injured neurons can be helped to survive, leading to better functional outcomes.

Such is the theory. Although it makes sense, in practice there is little high-quality evidence to support the practice of treating comatose survivors of cardiac arrest with anti-seizure medications.[4] Certainly it is known that particular discharge patterns such as GPDs are associated with poor outcomes.[5] Still, a discharging cortex is more likely to recover than one producing no brain waves at all. Will treating such patients with anti-seizure drugs help? The challenges to accumulating high-quality evidence in this population are legion. In the face of this ambiguity, practices vary dramatically from center to center. At some centers, feeling the need to do *something*, neurologists systematically monitor and treat nearly all such patients aggressively, while at others, the practice is considered futile.

The Treatment of Electroencephalographic Status Epilepticus After Cardiopulmonary Resuscitation (TELSTAR) trial is an open-label randomized control trial of 171 comatose survivors of cardiac arrest whose EEGs showed rhythmic and/or periodic patterns, comparing neurologic recovery between those whose patterns were treated or not.[6]

The inclusion criteria were patients who had been resuscitated following cardiac arrest, 18 years or older, with Glasgow Coma Scale (GCS) $\leq$8, for whom continuous EEG had been initiated less than 24 hours after return of spontaneous circulation. In the study population, the average age was 65 and most patients (79%) had GPDs, 10% had electrographic seizures, 3% had "evolving patterns," and 8% had other rhythmic and periodic patterns. Clinically, 62% had myoclonus. The mean GCS at randomization was 3.5 (Jeannette Hofmeijer, M.D. Ph.D., May 22 2022, personal communication with corresponding author), indicating profound coma.

Those randomized to the treatment group underwent an aggressive anti-seizure protocol under continuous EEG monitoring with sedation to suppress the offending EEG activity for at least 48 hours. Treating physicians had latitude in their choice of agents, with a flowchart to provide guidance. In the first step, an anti-seizure drug (usually phenytoin) was used in conjunction with infusion of a sedative (usually a benzodiazepine). When discharges continued, a propofol infusion was started and a second anti-seizure medication (typically levetiracetam or valproic acid) was started. Thiopental infusion was added if EEG activity persisted. In the trial, 73% of treatment patients required 2 or more anti-seizure medications and 99% received at least one sedative drug. Despite this treatment, a substantial proportion of patients never achieved activity suppression for 48 hours.

The primary study outcome was neurological disability based on a dichotomized Cerebral Performance Category (CPC) scale score at 3 months. The outcome was considered good when no to moderate neurological disability (CPC score 1-2) and poor if severe disability, coma, or death (CPC score 3-5).

Ultimately, the investigators found no significant difference between the treatment and standard-care group. A good outcome occurred in 10% and 8%, respectively; 80% and 82% of patients died in each group. Secondary outcomes of intensive care unit (ICU) stay duration and mechanical ventilation were slightly longer in the treatment group.

Comatose survivors of cardiac arrest are a medically complex and heterogenous group of patients. Studying this population is difficult for both conceptual and logistical reasons. The TELSTAR investigators successfully overcame these limitations to design and implement a high-quality trial that answers an important clinical question that neurologists face on a regular basis. The inclusion criteria were clear and rationally selected, the treatments painstakingly tracked, the presence of continuous EEG recordings allowed for careful observation of the effect of treatments, and the outcomes were collected in a blinded fashion. Considering the difficulty of introducing a trial in the ICU, and the necessity of maintaining communication with treating teams as well as with families during a desperate moment in the lives of their loved ones, the investigators should be applauded for their extraordinary accomplishment. Although the negative results are disappointing, knowing that aggressive anti-seizure treatment is not useful in this context will allow for better allocation of resources, and reduce patient suffering and family heartache in service of futile treatments.

Certain limitations of the trial must be taken into consideration, however, and care is necessary not to over-apply its lessons beyond the question that was studied. The authors mainly stress limitations related to the unblinded nature of the trial during the treatment phase, which could have affected care. For example, life-sustaining treatment was withdrawn early more often in the control group, probably in part because the treating team did not wish to interrupt a treatment in progress. The longer ICU stays in the treatment group also most likely reflect this difficulty.

Another potential limitation is that sedative drugs were central to the anti-seizure treatment, but these are often necessary for the treatment of ICU patients regardless of EEG activity. Although the treatment group received more sedation, 76% of control patients also received at least one sedative agent during the treatment period. If sedative drugs confer benefit, the patients in the control group could have benefitted as well. It is difficult to imagine how this problem could be avoided in an ethically designed trial. The impact of this limitation is, however, tempered by the fact that suppression of the offending EEG pattern was much more frequently observed in the treatment group than in the control group, clearly reflecting the effect of more aggressive anti-seizure medications on the EEG.

If suppression of the pattern is needed to achieve benefit, certainly the treatment group was different from the control group in this respect. Yet, this EEG benefit did not translate into a survival or functional outcome benefit.

Perhaps it was too much to expect of anti-seizure drugs that they could reverse death or disability in patients with such severe brain injury. Yet there may still be a role for them despite the TELSTAR results, which could be explored in subsequent trials. The treatment protocol was aggressive, and the difference between a good and poor primary outcome was stark. Although data are woefully lacking regarding the optimal treatment of periodic discharges in other clinical contexts, a general principle is that the aggressiveness of treatments must be individualized to the clinical circumstances of each patient, keeping in mind the potential harms of the treatment.[7] It might be that a less aggressive therapy, for example the use of an anti-seizure drug without sedation or the need to suppress the EEG pattern, might still offer a modest benefit among a selected proportion of patients with good outcomes. Compared to sedation, these drugs are less likely to cause harm and could have a neuroprotective effect that could be detected with neuropsychological testing, if not a CPC scale. Such questions are still amenable to further investigation.

Lastly, it is essential to remember that the trial patients were in profound coma. The treatment of patients who have suffered brain injury from cardiac arrest but are not comatose, or who have favorable EEG characteristics, for example those with so-called Pattern 2 early post-anoxic multifocal myoclonus[8] associated with vertex discharges that may show some periodicity, are associated with a continuous background, and carry a potentially favorable prognosis, cannot be inferred from the results of the present study.

In the meantime, although we are no longer bound to offer a treatment now shown to be futile, as always, neurologists must continue to evaluate each patient individually, keeping in mind all elements of the presentation, before considering appropriate interventions.

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