THE TERMINAL MAN—FROM SCIENCE FICTION TO THERAPY

Automated Seizure Abatement in Humans Using Electrical Stimulation

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The need for novel, efficacious, antiseizure therapies is widely acknowledged. This study investigates in humans the feasibility, safety, and efficacy of high-frequency electrical stimulation (HFES; 100–500 Hz) triggered by automated seizure detections. Eight patients were enrolled in this study, which consisted of a control and an experimental phase. HFES was delivered directly to the epileptogenic zone (local closed-loop) in four patients and indirectly, through anterior thalami (remote closed-loop), to the other four patients for every other automated seizure detection made by a validated algorithm. Interphase (control vs. experimental phase) and intraphase (stimulated vs. nonstimulated) comparisons of clinical seizure rate and relative severity (clinical and electrographic) were performed, and differences were assessed by using effect size. Patients were deemed "responders" if seizure rate was reduced by at least 50%; the remaining patients were deemed "nonresponders." All patients completed the study; rescue medications were not required; 1,491 HFESs (0.2% triggered afterdischarges) were included. Mean change in seizure rate in the local closed-loop group was −55.5% (−100 to +36.8%); three of four responders had a mean change of −86% (−100 to −58.8%). In the remote closed-loop, the mean change of seizure rate was −40.8% (−72.9 to +1.4%); two of four responders had a mean change of −74.3% (−75.6 to −72.9%). Mean effect size was zero in the local closed-loop (responders: beneficial and medium to large in magnitude) and negligible in the remote closed-loop group (responders: beneficial and medium to large). HFES effects on epileptogenic tissue were immediate and also outlasted the stimulation period. This study demonstrates the feasibility and short-term safety of automated HFES for seizure blockage and also raises the possibility that it may be beneficial in pharmacoresistant epilepsies.

COMMENTARY

The noted astronomer, Robert Jastrow, predicted in 1982 that someday everyone would need to carry briefcase-sized computers to cope with the increasing complexities of modern society. A mere 25 years later, bulky laptops are being replaced by slimmer PDAs (i.e., personal digital assistants). Meanwhile, the field of neuromodulation is perhaps the fastest growing area of neurosurgery, and a skull-mounted implantable computer attached to cortical electrodes is now available on an investigational basis for the treatment of intractable epilepsy. This truly is the dawn of a new age in neuroscience and neurotherapeutics, hastened by rapid advances in computer-processing speed and chip miniaturization. In addition, seizure-prediction algorithms have markedly improved over the past few years, permitting the early detection of seizure onsets, which allows a therapeutic intervention to occur immediately before ictal onset (1–3).

It has been clear for many years that the application of electric or magnetic fields to a seizure focus, either locally through direct cortical stimulation, or remotely to subcortical structures or cranial nerves, can influence the frequency and duration of both interictal and ictal events in animals and humans (4,5). However, although stimulation of the vagus and other cranial nerves is effective in reducing the frequency and severity of seizures through desynchronization of the cortical electroencephalogram (6), it is still unclear which patients will benefit. In addition, the efficacy of direct cortical stimulation might be vastly improved if it were combined with seizure-detection or closed-loop technologies with the capacity to deliver stimulation at the onset or even in advance of the ictal event (6). Such technology potentially could offer improved seizure control

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across a larger population of patients with intractable epilepsy, compared with vagal nerve stimulation alone. In addition, it is possible that neuromodulation could avoid the infrequent, but irreversible, neuropsychological sequellae of resective surgery and the side effects of antiepileptic medications.

Recently, several small studies have emerged in which open-loop (i.e., continuous, intermittent) or closed-loop (i.e., event-triggered) electrical stimulation has been delivered either remotely to the anterior thalamic nucleus or locally, that is, directly to seizure focus (7–9). In general, these open-label, nonrandomized studies have demonstrated the safety of this therapeutic modality and hinted at its potential efficacy. To this burgeoning literature, Osorio et al. (10) have added an elegantly designed study that simultaneously increases interest in the technique and raises far more questions than it answers.

A few aspects of the methods used by Osorio and colleagues warrant clarification. In brief, all eight patients included in the study underwent a control phase of video-EEG monitoring, involving implanted subdural and depth electrodes that localized epileptic foci and quantified seizure frequency, by using a seizure-detection algorithm. Thus, in theory, only patients with multifocal onsets were considered for remote stimulation ($n = 4$), whereas local therapy was delivered to patients with a precise, well-identified single focus ($n = 4$). The implanted intracranial electrodes also were used to record the electrographic response to therapy during the experimental phase of the study. The investigators used high-frequency stimulation, on the basis of data showing that high-frequency stimulation (100–500 Hz) is more likely to be inhibitory than is low-frequency stimulation (50–60 Hz). Only epileptiform events that were verified as true positive detections by an independent reviewer were analyzed for efficacy. Stimulation was applied to every other detected event so that the investigators could examine the effect of stimulation on events during which no stimulation occurred, to determine whether a carry-over effect occurred. In addition, antiepileptic drugs were kept equally as low during the experimental phase as they were during the control phase, thereby eliminating a drug effect.

Several remarkable findings emerged from this study. First, not only did two patients in the local-therapy group have complete elimination of their seizures, but in addition, the one patient who did not respond had bitemporal onsets and actually should not have been included in this arm of the study. More notable is the fact that all seizures that occurred in this patient did not come from the previously identified focus but rather from a new focus. Furthermore, within the entire local-therapy group, all seizures that occurred did so during periods when no stimulation occurred. Hence, when applied, local therapy eliminated 100% of local seizures! This result is almost too good to be true and clearly warrants further validation with a larger population of patients. For the remote-therapy group, the results are less impressive; however, the authors did find that therapy of longer duration ($\leq$30 seconds) appeared to be more effective than shorter-duration therapy. Finally, with respect to the carry-over effect, the authors report remarkable variability. In some patients for whom a direct therapeutic effect was identified, no carry-over was found, whereas in others for whom no direct effect was seen, a possible carry-over was identified. Hence, no conclusions can be drawn about antiepileptogenesis at this time.

Although the effect of direct stimulation is noteworthy, certain limitations to the study are apparent. First, the authors never present the efficacy data on their seizure-detection algorithm for the group of patients included in this study. False-positive and false-negative rates are critical bits of information that let the reader know how many seizures are being missed and how often stimulation is delivered unnecessarily. In addition, the group undergoing local therapy was clearly monitored for a shorter period during the experimental phase than during the control phase, which might have biased the results because it is well known that seizures can cluster. All patients in the remote stimulation arm had bitemporal mesial onsets, so efficacy for neocortical epilepsy remains unknown. In addition, the authors state that one of their inclusion criteria for this study was "good candidates for surgery," without any description of what factors would meet the criteria. Finally, a notable lack of any statistical evaluation of the findings exists.

Nevertheless, this study provides fairly convincing evidence that local stimulation may be quite effective in reducing the frequency of seizures. Outstanding questions remain. How close must electrodes be to the focus? What is the effect of stimulating during interictal versus ictal events? Are any benefits noted in quality of life or reduced mortality with this type of therapy? Would these patients be better off with a resection if their focus were in noneloquent cortex? As for the remote therapy, we must ask whether it offers any advantage over open- or even closed-loop vagal nerve stimulation to justify the added risk. Finally, will the financial incentives of the physicians and companies marketing these devices cloud their objectivity or, rather, provide incentive for needed progress?

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