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Does Deep Brain Stimulation Work in Lennox-Gastaut Syndrome? Well…it Depends

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DBS of Thalamic Centromedian Nucleus for Lennox–Gastaut Syndrome (ESTEL Trial)

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Objective: Prior uncontrolled studies have reported seizure reductions following deep brain stimulation (DBS) in patients with Lennox-Gastaut syndrome (LGS), but evidence from randomized controlled studies is lacking. We aimed to formally assess the efficacy and safety of DBS to the centromedian thalamic nucleus (CM) for the treatment of LGS. Methods: We conducted a prospective, double-blind, randomized study of continuous, cycling stimulation of CM-DBS, in patients with LGS. Following pre- and post-implantation periods, half received 3 months of stimulation (blinded phase), then all received 3 months of stimulation (unblinded phase). The primary outcome was the proportion of participants with $\geq$50% reduction in diary-recorded seizures in stimulated vs control participants, measured at the end of the blinded phase. A secondary outcome was the proportion of participants with a $\geq$50% reduction in electrographic seizures on 24-hour ambulatory electroencephalography (EEG) at the end of the blinded phase. Results: Between November 2017 and December 2019, 20 young adults with LGS (17-37 years;13 women) underwent bilateral CM-DBS at a single center in Australia, with 19 randomized (treatment, n = 10 and control, n = 9). Fifty percent of the stimulation group achieved $\geq$50% seizure reduction, compared with 22% of controls (odds ratio [OR] = 3.1, 95% confidence interval [CI] = .44-21.45, P = .25). For electrographic seizures, 59% of the stimulation group had $\geq$50% reduction at the end of the blinded phase, compared with none of the controls (OR= 23.25, 95% CI = 1.0-538.4, P = .05). Across all patients, median seizure reduction (baseline vs study exit) was 46.7% (interquartile range [IQR] = 28-67%) for diary recorded seizures and 53.8% (IQR = 27-73%) for electrographic seizures. Interpretation: CM-DBS in patients with LGS reduced electrographic rather than diary-recorded seizures, after 3 months of stimulation. Fifty percent of all participants had diary-recorded seizures reduced by half at the study exit, providing supporting evidence of the treatment effect.

Commentary

Lenox-Gastaut syndrome (LGS) is one of the most severe epilepsy phenotypes associated drug-resistant seizures and significant cognitive impairments. Following a few small studies suggesting promising benefits of DBS in LGS, the ESTEL Trial is the first prospective, double-blind, randomized study of continuous, cycling stimulation of DBS to the bilateral thalamic centromedian nucleus (CM-DBS) in LGS.[1]

Nineteen patients who received bilateral CM-DBS were randomized 3 months after implantation. In the blinded phase, 10 patients received stimulation for 3 months. Stimulation was then provided to all participants in a subsequent unblinded phase that lasted another 3 months.

In the blinded phase, higher responder rate (defined by $\geq$ 50% seizure reduction) based on EEG-recorded electrographic seizures was seen in the stimulation group compared to controls (89% vs 0%, OR= 23.25, 95% CI = 1.0-538.4, P = .05). At the 9 month post-implantation, the median EEG-recorded electrographic seizure reduction was 57% (95% CI = −1.15 to −.08, P = .027) between stimulation vs control groups. However, when assessed by diary-recorded seizures, neither the responder rate nor the median seizure reduction statistically differed between the groups. As observed in other studies, in the first 3 months following implantation, all patients had a seizure reduction regardless of DBS stimulation, possibly due to the

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"implantation effect". At the end of the trial (9 months post-implantation), a median reduction in diary-recorded and EEG-recorded seizures was 46.7% and 53.8%. The overall results from ESTEL trial suggest potential benefits of CM-DBS in LGS.

The role of neuromodulation in epilepsy treatment has expanded and offered different approaches in modulating a defined target and its associated circuitry, particularly in patients whom resective surgery deems unsuitable. The best evidence for DBS in epilepsy was gained after SANTE trial evaluating ANT-DBS in adults with drug-resistant focal epilepsy.[2] At 10 years of follow-up, ANT-DBS continued to show favorable efficacy and safety profiles.[3] In parallel, while CM-DBS faces some contradictory results on its seizure control efficacy, cumulative data suggest potential benefits in epilepsy with a generalized network.[4-6] A meta-analysis of 90 patients with CM-DBS showed a mean seizure reduction of 73.4% (95% CI 68.8 to 77.9, range 43.8% to 80.2%).[7] However, the lack of randomized-control studies with adequate power cast a shadow on CM-DBS role in epilepsy treatment. While diverse in causes, the electroclinical characteristics of LGS suggest an extensive network involving the thalamus and bilateral frontal and parietal cortices similar to generalized epilepsy, justifying the idea of CM-DBS target in LGS.[8,9]

DBS electrode target is one of the key challenges. Within the thalamus and each of its nuclei, a specific DBS target may be associated with superior treatment outcomes. The ESTEL trial group showed that accurate targeting of the CM is achievable using presurgical 3T MRI with magnetisation-prepared 2 rapid acquisition gradient-echoes (MP2RAGE) to delineate specific characteristics of CM.[10] Neurophysiologic biomarkers (eg EEG and local field potential) have been used to identify specific thalamic targets; however, we are far from fully understanding their characteristics and clinical implications.[4,10,11] Once again, LGS is heterogeneous in pathologies and epileptic networks that may evolve overtime. Therefore, it is plausible that specific etiology/network may be more responsive to DBS stimulation to a particular site given in a particular time window of network development. Stimulation parameters are another big complicated puzzle to solve. The most common parameters used in DBS studies in epilepsy (including ESTEL trial) are based upon the SANTE trial protocol (5V pulse amplitude, 145 Hz frequency, 90 μs pulse width, 1 min on 5 off cycling).[2] Specifically for CM-DBS, standard parameters are 2-6V, 60-130 Hz, 90-450 μs, intermittent or continuous.[12]

From ESTEL Trial, the differences in diary-recorded vs EEG-recorded seizures are worth discussing. One could suggest that the reduction in EEG-recorded electrographic seizures could potentially reduce seizure-associated comorbidities and contribute to an improved cognitive outcome. ESTEL trial did not demonstrate these impacts. While the seizure reduction was detected on EEG, the lack of appreciable effect on the caretaker end raises a question for its clinical meaningfulness. Diary-recorded seizures, while low cost, is cumbersome, and their accuracy has long been questioned. This trial emphasizes an important pitfall of seizure diary for clinical trials and calls for more accurate and objective seizure measurements.

ESTEL trial also evaluated cognition and adaptive behaviors using The Global Assessment of Severity of Epilepsy (GASE) Scale, Global Assessments of Disability (GADS), and Adaptive Behavior Assessment System (ABAS)-III. No significant change after DBS treatment was observed. While cognitive side effects from CM-DBS are not well known, mood and memory problems were reported in ANT-DBS.[3] It is conceivable that different thalamic structures likely differ in their role in cognition and mood. The long-term neuropsychological outcomes from CM-DBS remain to be further evaluated. Treatment adverse effects from ESTEL trial overall appear in line SANTE trial.[2]

Does DBS work in LGS? Well . . . it depends. Until we have a better proof, this question continues. Important areas remain to be understood. Optimizing patient selection, anatomical target, stimulation parameters, and neurophysiological biomarkers will help us better understand the appropriate utility of DBS in epilepsy. Improved seizure outcomes over time have been well documented in several DBS studies and believed to result from neuromodulation on neural plasticity, network reorganization, and improved stimulation programming.[3] Whether DBS work better than the cheaper more traditional approach of vagus nerve stimulation for LGS is another question that needs to be addressed. The long-term results from ESTEL cohort are to be followed.

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