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Is MORE better? Accumulating Evidence for ANT DBS in Epilepsy

Deep Brain Stimulation of the Anterior Nucleus of the Thalamus in Drug-Resistant Epilepsy in the MORE Multicenter Patient Registry

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Background and Objectives: The efficacy of deep brain stimulation of the anterior nucleus of the thalamus (ANT DBS) in patients with drug-resistant epilepsy (DRE) was demonstrated in the double-blind Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy randomized controlled trial. The Medtronic Registry for Epilepsy (MORE) aims to understand the safety and longer-term effectiveness of ANT DBS therapy in routine clinical practice. Methods: MORE is an observational registry collecting prospective and retrospective clinical data. Participants were at least 18 years old, with focal DRE recruited across 25 centers from 13 countries. They were followed for at least 2 years in terms of seizure frequency (SF), responder rate (RR), health-related quality of life (Quality of Life in Epilepsy Inventory 31), depression, and safety outcomes. Results: Of the 191 patients recruited, 170 (mean [SD] age of 35.6 [10.7] years, 43% female) were implanted with DBS therapy and met all eligibility criteria. At baseline, 38% of patients reported cognitive impairment. The median monthly SF decreased by 33.1% from 15.8 at baseline to 8.8 at 2 years ($p < 0.0001$) with 32.3% RR. In the subgroup of 47 patients who completed 5 years of follow-up, the median monthly SF decreased by 55.1% from 16 at baseline to 7.9 at 5 years ($p < 0.0001$) with 53.2% RR. High-volume centers (>10 implantations) had 42.8% reduction in median monthly SF by 2 years in comparison with 25.8% in low-volume center. In patients with cognitive impairment, the reduction in median monthly SF was 26.0% by 2 years compared with 36.1% in patients without cognitive impairment. The most frequently reported adverse events were changes (e.g., increased frequency/severity) in seizure (16%), memory impairment (patient-reported complaint, 15%), depressive mood (patient-reported complaint, 13%), and epilepsy (12%). One definite sudden unexpected death in epilepsy case was reported. Discussion: The MORE registry supports the effectiveness and safety of ANT DBS therapy in a real-world setting in the 2 years following implantation. Classification of Evidence: This study provides Class IV evidence that ANT DBS reduces the frequency of seizures in patients with drug-resistant focal epilepsy. Trial Registration Information: MORE ClinicalTrials.gov Identifier: NCT01521754, first posted on January 31, 2012.

Commentary

Three implantable neuromodulation therapies are approved for epilepsy, including 2 beyond the United States: anterior nucleus thalamic deep brain stimulation (ANT DBS) and vagus nerve stimulation (VNS). Anterior nucleus thalamic DBS has been approved in Europe since 2010 and in the United States since 2018. During the delay between approvals, 25 epilepsy centers from 13 European countries embarked on the first, large-scale observational postapproval study of DBS safety and outcomes known as Medtronic Registry for Epilepsy (MORE).[1] A total of 170 patients were implanted, with 155 patients followed for 2 years, and some extended to 5 years. This manufacturer-sponsored registry is the largest published study of patients with ANT DBS.

At 2 years, median seizure frequency reduction was 33%, reduced from 15.8/month to 8.8/month. The 50% or more responder rate was 32%; in contrast, 29% had no reduction in seizures. Five patients (3%) reported seizure freedom. Seizure

frequency reduction was better in centers that had performed 11 or more implants (43%) than in those with 10 or fewer (26%). Aside from center experience, no patient-specific markers predicted outcome; patients with baseline cognitive impairment had lower median reduction but this did not reach statistical significance. The presence of VNS did not affect outcomes. Mortality occurred in 1 patient (0.6%). Patients who were followed for 5 years had a more prominent reduction of 55% with a 53% responder rate; however only 47 remained for this duration.

The risk of acute complications was low and in line with other procedures for intracranial implantation. The most common patient-reported nonseizure side effects were memory impairment (15%) and depressive mood (13%). Although these concerns were also common at baseline (in 38% and 21% of subjects, respectively), the majority of patients who reported memory impairment and depressive mood as side effects did not report them before DBS, particularly for memory. One subject was explanted due to suicidal ideation. Changes to sleep quality were not reported to be a major side effect, a potential concern with regular stimulation of sleep structures.

MORE naturally draws comparisons to Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE),[2] which remains the only large double-blinded controlled study of ANT DBS. SANTE included 110 subjects of whom 81 had 2 years of follow-up and 57 maintained extended follow-up for 10 years. MORE is suggested by the authors to be more comparable to real-world data. Median seizure reduction in MORE was worse than in SANTE at the same time point of 2 years (33% vs 56%, respectively). The 50% responder rates were also worse at 32% for MORE versus 56% for SANTE. The discrepancy remained at 5 years (seizure frequency reduction of 55% vs 69%, and responder rate of 53% vs 68%).[3] The reasons for this discrepancy are not clear. Epilepsy localization (mostly temporal and frontal) and severity (including duration, frequency, and seizure types) were similar. Although MORE suggested center experience mattered, all centers in MORE had the benefit of published SANTE experience regarding electrode implantation and programming. Unlike MORE, half of the patients in SANTE had stimulation delayed due to the initial control randomization; this probably washed out by 2 years, and if not, would have been expected to favor the MORE subjects. There were 24 patients in MORE with active VNS, unlike in SANTE where VNS devices required removal; however, it is unlikely this explains the difference due to the low proportion of patients in this group, and because VNS did not affect outcomes in MORE. The seemingly worse real-world outcomes with DBS differ from initial, not yet peer-reviewed reports of responsive neurostimulation (RNS), in which real-world observational results have been better than the initial trial experience.[4] Further trials will be required for a more accurate picture of clinical response, and more importantly, if potential responders can be identified before implantation.

MORE and SANTE had similar side effect profiles with memory impairment and depression being the major concerns. In SANTE, these were seen disproportionately in the active stimulation group compared with the control group, suggesting the effects are not due to implant or placebo effects. However, formally measured memory scores and depression inventories at 1 to 2 years did not show impairments,[5] suggesting these effects may be transient and/or reflect functions not measured by standard evaluations. These issues are common in people with epilepsy, and the potential for new or further impairment may steer some patients and providers toward other treatment modalities. Alternatively, there may be implantation strategies and programming settings that can avoid these effects.

Of the approved neuromodulation therapies, VNS has been available longest, is most widely available, and is the only one that does not require intracranial surgery. Direct comparisons between DBS and VNS must be undertaken with caution, however, and have limited validity, as there have been no head-to-head trials.[6] Efficacy estimates for VNS have been variable, as appears to be the case with DBS. To date, 3 adult and 1 pediatric randomized controlled trials of VNS had seizure reductions of 22% to 43%. Studies that did not reach statistical significance had fewer patients, suggesting a sample size effect. Additionally, multiple, uncontrolled studies of VNS with longer term follow-up suggests a cumulative benefit with time, but have been uncontrolled and subject to biases. Importantly, MORE suggests opting for VNS does not bar future DBS success.

MORE continues to support ANT DBS as beneficial in some patients; however patients with a clear response may be limited, are not known in advance, and are at risk of neuropsychiatric side effects that, although possibly transient and subjective, have not frequently been reported with other neuromodulation therapies. These concerns suggest ANT DBS should be carefully considered before implantation. A sponsored US postapproval study is underway that may help clarify concerns. There are no head-to-head trials of DBS with either VNS or RNS. Such trials are likely to present logistical and ethical difficulties and would probably require government funding.

Within the field of thalamic stimulation, many questions remain as to the optimal neuromodulation strategy. There is only speculation concerning the best nucleus to target in any individual. The mechanisms by which thalamic stimulation reduces seizures and may cause side effects remain uncertain. Stimulation parameters and waveforms are not evidence-based, and there is no clear strategy to optimize them. The approved ANT DBS system is open-loop, and it is unknown whether closed-loop thalamic stimulation would offer better efficacy or fewer side effects. The currently available RNS platform provides extensive data to monitor epilepsy burden and guide therapy[7]; it is unknown whether thalamic recordings, now available in limited form and situations, can provide similar benefits. Each of these topics would be worthy of detailed investigation and could help improve response rates beyond the modest effects seen to date and potentially improve tolerability.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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