Epilepsy Currents
2021, Vol. 21(5) 334–336

DOI: 10.1177/15357597211029169
journals.sagepub.com/home/epi
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Cheers for SANTÉ: Long Term Safety and Efficacy of Anterior Nucleus of the Thalamus DBS

The SANTÉ Study at 10 Years of Follow-Up: Effectiveness, Safety, and Sudden Unexpected Death in Epilepsy

Salanova V, Sperling MR, Gross RE, et al. *Epilepsia*. 2021;62:1306-1317. doi:10.1111/epi.16895

Objective: We evaluated the efficacy and safety of deep brain anterior thalamus stimulation after 7 and 10 years and report the incidence of sudden unexpected death in epilepsy (SUDEP) and overall mortality in adults in the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTÉ) study. Methods: After the 3-month blinded and 9-month unblinded phases, subjects continued to be assessed during long-term follow-up (LTFU) and later a continued therapy access phase (CAP), to further characterize adverse events and the incidence of SUDEP. Stimulus parameter and medication changes were allowed. Results: One hundred ten implanted subjects accumulated a total of 938 device-years of experience (69 subjects during the LTFU phase and 61 subjects in the CAP phase). Prior to study closure, 57 active subjects continued therapy at 14 study centers, with follow-up of at least 10 (maximum 14) years. At 7 years, median seizure frequency percent reduction from baseline was 75% ($P < .001$), with no outcome differences related to prior vagus nerve stimulation or resective surgery. The most severe seizure type, focal to bilateral tonic–clonic, was reduced by 71%. Adding new antiseizure medications did not impact the pattern of seizure reduction over time. There were no unanticipated serious adverse events in the study. The definite-plus-probable SUDEP rate, based on SANTÉ study experience (2 deaths in 938 years) and previous pilot studies (0 deaths in 76 years), indicated a rate of 2.0 deaths for 1000 person-years. Overall mortality was 6.9 deaths per 1000 person-years. Significance: The long-term efficacy and safety profiles of the deep brain stimulation (DBS) system for epilepsy are favorable and demonstrate stable outcomes. Improvement in frequency of the most severe seizure type may reduce SUDEP risk. The SUDEP rate with DBS (2.0) is comparable to other neuromodulation treatments (ie, vagus nerve stimulation, responsive neurostimulation) for drug-resistant focal epilepsy.

Commentary

In the United States, the FDA has approved 3 neuromodulation devices for the treatment of drug-resistant epilepsy. Vagal nerve stimulation (VNS), responsive neurostimulation (RNS), and deep brain stimulation of the anterior nucleus of thalamus (DBS ANT) are indicated for the treatment of patients with focal-onset seizures who are not good candidates for surgical or ablative treatment. The devices differ in the location where the stimulating electrode(s) are implanted and in the method of delivering electrical stimulation, ie, open or preset vs closed loop or responsive to a specific electrographic (cerebral or cardiac) signal. Despite these differences, the efficacy observed during the blinded portion of their pivotal trials was similar among the 3 modalities. And although few patients become seizure free following stabilization of the stimulation parameters, all 3 modalities have shown a reduction in the incidence of sudden unexpected death in epilepsy (SUDEP) and improvement in quality-of-life measures.[1-3]

The Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTÉ) pivotal study demonstrated efficacy in a multicenter, double-blind, randomized, sham-controlled trial of drug resistant patients.[3] Open loop stimulation with preset parameters, in addition to medical therapy, was delivered to both thalami with the option to continue in an open label extension. At the end of the blinded phase (3 months after implant), median seizure frequency reduction was 40.4% in the treated group compared to 14.5% in the control group. Almost all patients continued onto the long-term follow-up of 2 years. Recently, the long-term efficacy and safety of ANT DBS of patients who were followed for at least 7 years and some for 10 years was reported.[4] Of the initial cohort of 110 patients, 73 were followed with office visits every 6 months along with monthly diary collection. Antiseizure drugs and neurostimulation settings could be changed at the discretion of the clinician, with only 1 subject remaining on the original SANTÉ settings, but with limitation on the charge density that could be delivered. For most patients, higher stimulation settings were used in the amplitude and duty cycle, translating into a median battery life of 35.4 months. When battery depletions occurred, seizure frequency did not increase suggesting the existence of a

disease-modifying effect. Importantly, decreases in impedance from the active DBS contacts were seen in 88.5% of subjects.

Long-term retention at 7 years was 66% with discontinuations primarily due to lack of benefit (24%), death (6%) and implant site infection (5%). The mean responder rate, defined as a ≥50% reduction in seizure frequency, was 74% with 8% of patients achieving seizure-freedom for more than 2 years. To assess the potential impact of missing data on the results, last observation carried forward and other sensitivity measures were performed. Controlling for patient attrition, the addition of new ASDs, prior VNS therapy or the location of the epileptogenic zone had minimal impact on the results. This last factor diverged from the results of the pivotal trial, where higher efficacy was seen in patients with uni- or bi-temporal lobe seizure onsets.

Regarding adverse events (AEs), depression was reported in 37.3% of subjects, 2/3 of whom had a preexisting history of depression, and suicidality in 10%. Memory impairment was reported in 30% of subjects, 50% of whom had preexisting deficits, but formal neuropsychological testing was not performed. Despite the high incidence of these AEs, few discontinuations were observed. Nevertheless, it is somewhat concerning that the presence of mood disorders, which are common comorbidities in drug-resistant epilepsy, might limit the use of this therapy. Additionally, de-novo paranoia and anxiety symptoms have been reported in a few patients without pre-existent mood disorders.[5] In terms of mortality, there were 2 definite and 1 possible, deaths that were attributed to SUDEP. This represents a SUDEP rate of 2 deaths per 1000 person-years, which is below the reported rate of 6.3-9.3 per 1000 person-years in patients with drug-resistant epilepsy.[6]

Limitations of the study include the lack of a control group, the effect of discontinuations of subjects with a poor response, changes in medication and/or lifestyle with the potential to improve seizure control and lack of power to assess SUDEP rate variations. Conversely, the authors should be commended on achieving a high retention rate prior to study closure.

These data suggest that VNS and ANT DBS might be complimentary therapies as illustrated by the high responder rate found in the SANTÈ trial despite previous treatment with VNS. This finding is not surprising given that the techniques presumably modulate or desynchronize different nodes of the neural networks involved in the epileptogenic process.[7,8] Intriguingly, a newly approved iteration of the Medtronic DBS device has the potential to provide closed-loop stimulation by recording ongoing thalamic background local field potential and triggering stimulation upon detection of a thalamic "signature" that relates to epileptiform activity.[9,10]

While the study by Salanova et al[4] demonstrates that the efficacy of ANT DBS improves over time, with acceptable safety and tolerability, important questions remain unanswered. What are the optimum thalamic stimulation parameters? Would targeting and stimulating different thalamic nuclei based on the lobar localization of the epileptogenic focus result in better efficacy? For instance, a recent study indicated that the medial pulvinar nucleus frequently participated in focal seizures, with early involvement in seizure generation, in a subset of patients with epileptogenic foci localized to different regions and of mixed etiologies.[11] Are there different thalamic nuclei that should be targeted depending on the epileptic syndrome, ie, localization-related vs symptomatic generalized epilepsy? Can the incidence of adverse effects on mood and cognition be minimized by differential stimulation paradigms/targets? Might there be a differential response between open and (potentially) closed-loop thalamic stimulation? Finally, are there differences in efficacy between the different neuromodulation therapies? Remarkably, the long-term efficacy of RNS is reported to be extraordinarily similar to that of ANT DBS.[12] Until comparative trials are performed, it will be impossible to answer the question of whether there are differences in the efficacy between the different neuromodulation modalities. In the meantime, lets cheer à votre SANTÈ!

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