Vagus nerve stimulation for drug-resistant epilepsy

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see also Responsive neurostimulation.

Vagus nerve stimulation for drug-resistant epilepsy was first approved in Europe in 1994 and in the United States (US) in 1997. Subsequent modifications improved the safety and the efficacy of the system. The most recent application of vagal neurostimulation is represented by transcutaneous devices that are claimed to have strong therapeutic potential.

Indications

Vagus nerve stimulation for drug-resistant epilepsy indications.

Mechanism of action

The use of functional neuroimaging such as SPECT, PET and fMRI in patients undergoing peripheral nerve stimulation can help us to understand these mechanisms.

Bari et al., reviewed the literature for functional neuroimaging performed in patients implanted with peripheral nerve stimulators. These studies suggest that brain activity in response to peripheral nerve stimulation is a complex interaction between the stimulation parameters, disease type and severity, chronicity of stimulation, as well as nonspecific effects. From this information we may be able to understand which brain structures are involved in the mechanism of peripheral nerve stimulation as well as define the neural substrates underlying these disorders [1].

Effectiveness, safety, and cost

Connor et al., performed a review of available literature published between 1980 and 2010. Inclusion criteria for articles included more than 10 patients evaluated, average follow-up of 1 or more years, inclusion of medically refractory epilepsy, and consistent preoperative surgical evaluation. Articles were divided into 4 classes of evidence according to criteria established by the American Academy of Neurology.

A total of 70 publications were reviewed, of which 20 were selected for review based on inclusion and exclusion criteria. There were 2 articles that provided Class I evidence, 7 that met criteria for Class II evidence, and 11 that provided Class III evidence. The majority of evidence supports VNS usage in partial epilepsy with a seizure reduction of 50% or more in the majority of cases and freedom from seizure in 6%-27% of patients who responded to stimulation. High stimulation with a gradual increase in VNS stimulation over the first 6 weeks to 3 months postoperatively is well supported by Class I and II data. Predictors of positive response included absence of bilateral interictal epileptiform activity and cortical malformations.

Vagal nerve stimulation is a safe and effective alternative for adult and pediatric populations with epilepsy refractory to medical and other surgical management [2)].

A study looked at the research available on the effectiveness, safety, and cost of two types of Electrostimulation devices currently licensed for treatment of epilepsy for adults and children in Canada: vagus nerve stimulation (VNS) and deep brain stimulation (DBS). Both approaches appear to be effective at reducing the frequency of seizures in adults. However, the evidence on DBS is limited to a single study with adults; Chambers and Bowen found no studies of DBS with children. Studies on VNS showed that both adults and children had fewer hospitalizations and emergency department visits after the procedure. Both procedures carry serious risks, but several longer-term studies have found that adverse events appear to be limited. The cost of VNS, including the process of assessing whether or not patients are good candidates for the procedure, is estimated to be about $40,000 per person (and higher for DBS because the device is more expensive and the operating time is longer). Of the 70,000 people in Ontario with epilepsy, about 1,400 (300 children and 1,110 adults) may be candidates for VNS to reduce their seizures [3)].

Complications

Complications and failure of the device can result from lead fracture, device malfunction, disconnection, or battery displacement and can result in a variety of symptoms.

D'Agostino et al., present an interesting case of stimulator malfunction with increased impedance change seen only with a change in head position.

The patient is a 25-year-old male with a vagal nerve stimulator (VNs) placed for medically refractory epilepsy who presented with neck pain and an electrical pulling sensation in his neck whenever he turned his head to the right. Initial interrogation of the VNs showed normal impedance. Subsequent interrogation with the patient's head turned found increased impedance only when the head was

turned to the right. The patient had successful removal and replacement of the device with resolution of his preoperative complaints. Partial lead fracture was seen at explant.

Vagus nerve stimulator malfunction can present in atypical ways. Positional maneuvers may help with its timely diagnosis [4].

Outcome

It is still difficult to predict which patients will respond to VNS treatment and to what extent.

Liu et al., aimed to explore the relationship between preoperative heart rate variability (HRV) and VNS outcome. 50 healthy control subjects and 63 DRE patients who had received VNS implants and had at least one year of follow up were included. The preoperative HRV were analyzed by traditional linear methods and heart rhythm complexity analyses with multiscale entropy (MSE). DRE patients had significantly lower complexity indices (CI) as well as traditional linear HRV measurements than healthy controls. We also found that non-responders0 had significantly lower preoperative CI including Area 1-5, Area 6-15 and Area 6-20 than those in the responders0 while those of the non-responders50 had significantly lower RMSSD, pNN50, VLF, LF, HF, TP and LF/HF than the responders50. In receiver operating characteristic (ROC) curve analysis, Area 6-20 and RMSSD had the greatest discriminatory power for the responders0 and non-responders0, responders50 and non-responders50, respectively. Our results suggest that preoperative assessment of HRV by linear and MSE analysis can help in predicting VNS outcomes in patients with DRE [5].

Data suggest that sudden unexpected death in epilepsy patients (SUDEP) risk significantly decreases during long-term follow-up of patients with refractory epilepsy receiving VNS Therapy. This finding might reflect several factors, including the natural long-term dynamic of SUDEP rate, attrition, and the impact of VNS Therapy. The role of each of these factors cannot be confirmed due to the limitations of the study [6].

Systematic reviews

To analyze the efficacy and safety of high-frequency VNS versus control (low-frequency VNS or no VNS) in patients with DRE using data from randomized controlled trials (RCTs). An electronic literature search was conducted on PubMed, EMBASE, and Cochrane Controlled Register of Trials (CENTRAL); 12 RCTs reporting seizure frequency or treatment response in studies containing a high-frequency VNS treatment arm (conventional VNS or transcutaneous VNS [tVNS]) compared to control (low-frequency VNS or no VNS) were included. Seizure frequency, treatment response (number of patients with ≥ 50% reduction in seizure frequency), quality of life (QOL), and adverse effects were analyzed. Seizure frequency was reported in 9 studies (718 patients). Meta-analysis with random-effects models favored high-frequency VNS over control (standardized mean difference = 0.82, 95%-CI = 0.39-1.24, $p < .001$). This remained significant for subgroup analyses of low-frequency VNS as the control, VNS modality, and after removing studies with moderate-to-high risk of bias. Treatment response was reported in 8 studies (758 patients). Random-effects models favored high-frequency VNS over control (risk ratio = 1.57, 95%-CI = 1.19-2.07, $p < .001$). QOL outcomes were reported descriptively in 4 studies (363 patients), and adverse events were reported in 11 studies (875 patients). Major side

effects and death were not observed to be more common in high-frequency VNS compared to control. High-frequency VNS results in reduced seizure frequency and improved treatment response compared to control (low-frequency VNS or no VNS) in patients with drug-resistant epilepsy. Greater consideration for VNS in patients with DRE may be warranted to decrease seizure frequency in the management of these patients [7].

For vagus nerve stimulation (VNS), there is moderate-quality evidence for its effectiveness in adults with drug-resistant partial epilepsies. Moderate-to-low-quality evidence supports the efficacy and safety of deep brain stimulation (DBS) and responsive neurostimulation (RNS) in patients with DRE. There is moderate-to-very low-quality evidence that transcranial direct current stimulation (tDCS) is effective or well tolerated. For transcutaneous vagus nerve stimulation (tVNS), transcranial magnetic stimulation (TMS) and trigeminal nerve stimulation (TNS), there are insufficient data to support the efficacy of any of these modalities for DRE. These treatment modalities, nevertheless, appear well tolerated, with no severe adverse events reported.

Head-to-head comparison of treatment modalities such as VNS, DBS and RNS across different epileptic syndromes are required to decide which treatment modality is the most effective for a given patient scenario. Such studies are challenging and it is unlikely that data will be available in the near future. Additional data collection on potentially promising noninvasive neurostimulation modalities like tVNS, TMS, TNS and tDCS is warranted to get a more precise estimate of their therapeutic benefit and long-term safety [8].

Critical reviews

In a review, Toffa et al. sought to analyze the most meaningful available data describing the indications, safety and efficacy of the different approaches of VNS in clinical practice. Therefore, they identified studies reporting VNS efficacy and/or safety in epilepsy and its comorbidities from January 1990 to February 2020 from various databases including PubMed, Scopus, Cochrane, US government databases and VNS manufacturer published resources. In general, VNS efficacy becomes optimal around the sixth month of treatment and a 50-100 % seizure frequency reduction is achieved in approximately 45-65 % of the patients. However, some clinically relevant differences have been reported with specific factors such as epilepsy etiology or epilepsy classification, patient age as well as the delay of VNS therapy onset. VNS efficacy on seizure frequency has been demonstrated in both children and adults, in lesional and non-lesional cases, in focal and generalized epilepsies, on both seizures and epilepsy comorbidities. Regarding the latter, VNS can lead to an improvement of about 25-35 % in depression scores, 35 % in anxiety scores and 25 % in mood assessment scores. If non-invasive devices are undeniably safer, their efficacy is limited due to the scarcity of large cohort studies and the disparity of methodological approaches (study design and stimulation parameters). Overall, they believe that there is a progress margin for improving the safety of implantable devices and, above all, the effectiveness of the various VNS approaches [9]. Boon et al., conducted a systematic review on the currently available neurostimulation modalities primarily with regard to effectiveness and safety.

Case series

see Vagus nerve stimulation for drug resistant epilepsy case series.

Case reports

Arhan et al., describe the first child with drug-resistant epilepsy in whom vagus nerve stimulation aggravated seizures and emerged status epilepticus after the increase in vagal nerve stimulation current output.

A 13-year-old girl presented with refractory secondary generalized focal epilepsy. Vagal nerve stimulator was implanted because of drug-resistant epilepsy. After the increase of vagal nerve stimulator current output to a relatively high level, the patient experienced seizure aggravation and status epilepticus.

They conclude that vagus nerve stimulation may induce paradoxical seizures and may lead to status epilepticus, similarly to some antiepileptic drugs [10].

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