Neurostimulation

A promising therapeutic option for medically refractory epilepsy

Ali Hassan, *MBBS, FCPS,* ***Khalid W. Al-Quliti,*** *MBBS, MD.*

ABSTRACT

الصرع هو أحد اضطرابات الجهاز العصبي الشائعة والمزمنة ويصيب نحو 65 مليون شخص حول العالم وعلى الرغم من التقدم العلمي في العلاج الدوائي للصرع لايزال هناك ما يقارب من 30% من المرضى يعانون من حالات الصرع المستعصية دوائياً وفي تلك الحالات يعتبر من الضروري البحث عن وسائل علاجية بديلة. يمكن لجراحة الصرع عن طريق إزالة البؤر الصرعية أن تكون بديلاً علاجياً مناسباً لكثير من المرضى للتحكم في نوبات الصرع ولكن هذه العمليات الجراحية لا تناسب جميع مرضى الصرع المستعصي دوائياً. يعتبر التحفيز الكهربائي للدماغ أحد الأساليب الحديثة والمتطورة سريعاً لعلاج حالات التشنجات الصرعية المستعصية للعلاج الدوائي والجراحي وذلك عن طريق تحفيز العصب المبهم، التحفيز العميق للمخ من نواة المهاد الأمامية، أو التحفيز العصبي الإستجابي وهذه الأساليب أظهرت نتائج إيجابية ودعم بأدلة علمية من فئة 1 لاستخدامها عند المرضى الذين يعانون من الصرع المستعصي للعلاج الدوائي. وفي هذا الاستعراض سنقوم بمناقشة الأدلة العلمية لأساليب التحفيز الكهربائي العلاجي وآلية طرق عملها وفعاليتها ونتائجها وتطبيقها في الاستخدام السريري.

Epilepsy is a common and serious chronic neurological disorder, affecting around 65 million people worldwide. Despite the advances in pharmacologic treatments for epilepsy, approximately 30% of the patients remain medically refractory and continue to have seizures on medications, in such cases, other treatment approaches are necessary. Resection surgery can be an alternative in many patients to achieve good seizure control; however, not all patients are suitable candidates for surgery. Electrical stimulation of the brain is a rapidly evolving therapy for patients with uncontrolled seizures despite the best medical and surgical treatment. Vagus nerve stimulation, deep brain stimulation of the anterior nucleus of thalamus, and responsive neurostimulation have class I evidence supporting their use in patients with intractable epilepsy. In this review, we discuss the evidence of these therapeutic modalities, their mechanism of action, efficacy, outcome, and their application in clinical use.

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From the Section of Neurology (Hassan, Al-Quliti), Department of Medicine, College of Medicine, Taibah University, and the Department of Neurology (Al-Quliti), King Fahad Hospital, Madinah Munawarah, Kingdom of Saudi Arabia.

Address correspondence and reprint request to: Dr. Khalid W. Al-Quliti, Chairman, Section of Neurology, Department of Medicine, College of Medicine, Taibah University, PO Box 51099, Madinah Munawarah 41543, Kingdom of Saudi Arabia. Tel. +966 (14) 8618888 Ext. 3060. Fax. +966 (14) 8618023 Ext. 8189. E-mail: kh_alquliti@yahoo.com

Epilepsy is a devastating disease, and the third most common neurological disorder,[1] and with an annual incidence of 50/100,000 people, nearly 1% of the population suffers from epilepsy worldwide.[1] Medically refractory epilepsy (MRE), which was recently defined by the International League Against Epilepsy as "failure of adequate trials of 2 tolerated and appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom," poses significant psychological, financial, and physical burdens on patients and their families.[2] Despite the impressive recent advances in AED therapies, around 30% of the patients remain medically refractory.[3] The resection of the epileptogenic focus is the most effective surgical treatment for this population.[4] However, many patients are not candidates for surgery, or whose seizures were not substantially improved by prior intracranial epilepsy surgery, or who are opposed to intracranial surgery.[5] Neurostimulation is a rapidly expanding and emerging field in epileptology with the potential to improve the

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quality of life and occasionally be curative in patients with MRE. Class I evidence supporting the use of 3 modalities of neurostimulation: vagus nerve stimulation (VNS), deep brain stimulation (DBS) of the anterior nucleus of thalamus (ANT), and most recently the advanced responsive neurostimulation system (RNS) via a closed-loop device.[6-8] Of these modalities, only VNS has been approved by the Food and Drug Administration (FDA), while the European Medicinal Agency (EMA), has approved both VNS and DBS of ANT for the treatment of MRE.[6-8] From a therapeutic point of view, neurostimulation can be divided into 2 basic subgroups, (1) programmed or chronic stimulation (for example VNS, or DBS of ANT) that delivers recurrent therapy to a site and potentially modulates seizure activity, and (2) responsive stimulation, that is designed to respond to the seizure activity and to deliver electrical therapy in response to this activity.[5] Our purpose in this review article is to discuss the results of related clinical trials for each treatment modality, understand the mechanism of action, efficacy, outcomes, and associated adverse effects as well as to delineate which set of patients might benefit most from each. Vagal nerve stimulation is discussed in more detail as it is being practiced largely worldwide, including in the Kingdom of Saudi Arabia.

Vagal nerve stimulation. Vagal nerve stimulation is the most frequently used neurostimulation modality for MRE. Human treatment with VNS began in 1988, it gained approval in Europe in 1994, and in the United States in 1997 for adjunctive treatment of medically refractory focal onset seizures in adults and children over 12 years of age,[6] and while and since then the system has been implanted in more than 65,000 individuals worldwide and being used in 70 countries.[6,9]

Therapeutic mechanism. The exact mechanism by which VNS reduces seizure frequency is not fully understood. The vagus nerve has a widespread connection in the different areas of the brain.[10] Vagal nerve stimulation therapy is designed to stimulate the peripheral vagus nerve, which is composed of 80% afferent fibers that terminate in the nucleus of the tractus solitarius.[11] The tractus solitarius converges to the parabrachial nucleus of pons, that projects to the hippocampus, amygdala, and hypothalamus that are known to play key roles in seizure onset and propagation.[12] Functional MRI and positron emission tomography (PET) studies have revealed the widespread increase in CNS metabolism mainly in the cerebral cortex, limbic system, thalamus, hypothalamus, cerebellum, and medulla as a result of peripheral stimulation of the vagus nerve.[13] Unilateral stimulation of the vagal nerve produces bilateral afferent responses. Therefore, right vagal stimulation is as effective as left sided stimulation, and no greater benefit was seen with the stimulation when provided bilaterally.[14,15] The right vagus nerve provides more innervations to the cardiac atria, so in clinical practice the left sided vagus nerve is generally used to avoid adverse cardiac effects.[16]

Suitable candidates. While optimal candidates for VNS have yet to be identified, the FDA has approved VNS as an adjunctive therapy of focal onset seizures refractory to AED in patients over 12 years of age.[6] Clinical practice often extends beyond official guidelines, and this is true for VNS. In specialized epilepsy centers, the use of VNS not only has been tested in children younger than 12 years, its use has also been extended beyond just partial seizures.[17] There is accumulating evidence that VNS is beneficial in other epilepsy syndromes such as Lennox-Gastaut syndrome, and idiopathic generalized epilepsies.[18-20] Before being evaluated for VNS placement, a search for a resectable focus should be undertaken. Certain syndromes such as mesial temporal lobe epilepsies are likely to benefit substantially from resective surgery, and yield a higher likelihood of seizure cessation.[14,21-23]

Implantation. The NeuroCybernetic prosthesis (Cyberonics Inc., Houston, TX, USA) (**Figure 1**) is implanted under the skin of the upper left chest and consists of an electronic generator that delivers

Figure 1 - Vagal nerve stimulator (Courtesy of Cyberonics Inc., Houston, TX, USA).

stimulation through a flexible bipolar lead that attaches to the vagus nerve in the neck. The generator is then programmed externally with a programming wand, attached to a personal computer.[24] A typical treatment regimen is intermittent stimulation that is delivered every 5 to 10 minutes for 30 seconds throughout the day and night.[24] In addition to its "round-the-clock" pattern of stimulation, there is another mode of stimulation that is activated by a hand-held magnet, provided to patients, when they experience an aura or simple partial seizures.[25] This mode of use may help to attenuate threatened seizures. However, the magnet function seems to be useful in around 30-40% of patients.[26] Battery life is dependent on the settings used, and usually lasts for 8-12 years. The higher the frequency and output of the settings, the faster the battery will run down. The generator must be replaced when the battery life wanes.[24]

Efficacy and outcome. Complete seizure freedom is rarely achieved using VNS. In a recent meta-analysis of VNS efficacy in epilepsy[27] comprising 74 clinical studies with 3321 patients suffering from MRE, it was identified that after VNS, seizure frequency was reduced by an average of 45%, with a 36% reduction in seizures frequency within one year, and 51% reduction after one year of treatment. Tuberous sclerosis and posttraumatic epilepsy were shown to be positive predictors of favorable outcome in this meta-analysis.[25] Another analysis of 65 epileptic patients who received VNS therapy for more than 10 years, recognized a progressively increasing response, with a mean decrease in frequency of seizure at one year of 36%, while at 4 years it was 58%, at 8 years was 66%, and after 10 years it was 76%.[28] Another analysis in the same center in 436 adults and children with MRE, treated with VNS for a mean duration of 4.9 years identified a mean seizure frequency reduction of 56%.[29] In the United States, 5 multicenter trials have been conducted. (E01-E05).[30-34] The E03[32] and E05[34] were randomized, double-blind clinical trials investigating the efficacy of VNS. In these trials, 2 stimulation parameters were applied and high-frequency stimulation (30 Hz, 500 ms pulse width, 30 seconds on, 5 minutes off) was found to be more effective.

Safety and side effects. The safety and tolerability of VNS has been also found to be good in over 65,000 patients available for long-term follow-up worldwide.[24] The reported intraoperative adverse effects for VNS are very low and often not serious.[24] The common side effects of VNS in the acute phase after implantation include intermittent hoarseness (28%), cough (14%), voice alteration (13%), tingling and pain (12%), headache (4.5%), and dyspnea (3.2%) that occurs only with stimulation,[18,35] and with mild to moderate severity.[36] Rarely, clinically significant alterations in cardiac rhythms, pulmonary function, or gastrointestinal motility, or secretions are seen.[36] Worsening of preexisting obstructive sleep apnea has also been reported.[37]

Deep brain stimulation. Deep brain stimulation with a target of the ANT has recently been approved for the treatment of epilepsy in Europe,[38] and is waiting for FDA approval as further risk-benefit analysis and investigations into which patient populations may benefit most are required.

Therapeutic mechanism. Like VNS, the exact mechanism by which DBS reduces seizure activity is not completely understood. The ANT is part of the classic circuit of Papez,[39] and this circuit has been shown to play a key role in the generation and propagation of epileptic activity.[40,41] High-frequency stimulation applied to a nucleus in the circuit of Papez inhibits seizure propagation and halts spread to the neocortex.[8] Stimulating the ANT to suppress the seizures has been attempted in many studies with varying degrees of success.[34,42-44] Moreover, researchers have found that lesions of the ANT resulted in improved seizure control in human patients.[45]

Suitable candidates. In Europe, DBS of the ANT has been approved as an adjunctive therapy for MRE of focal onset in adult patients of 18 to 65 years old, with significantly impaired quality of life for at least 12-18 months.[8] It is also recommended to first consider both resection surgeries of epileptogenic focus and VNS before proceeding with DBS.[46] Deep brain stimulation has not yet been tested in children. It may serve as a potential treatment for severe childhood epilepsies in the future.[9,47]

Implantation. Deep brain stimulator (**Figure 2**) electrodes are implanted bilaterally in the anterior nuclei of the thalamus. The stimulator and battery are implanted under the left clavicle, where it is accessible for adjusting the parameters used.[8]

Efficacy and outcome. Like VNS, complete seizure freedom is rarely achieved using DBS. Recently, a large randomized controlled trial, the Electrical Stimulation of the Anterior Nucleus of Thalamus for Epilepsy (SANTE) trial,[8] demonstrated a significant reduction in mean seizure frequency with ANT stimulation. These were highly refractory patients, 54% had previous epilepsy surgery or VNS therapy. During the 3 month blinded phase of the SANTE trial, the entire treatment group had a significant 38% reduction, compared with 14.5% in the placebo group. The SANTE Trial also

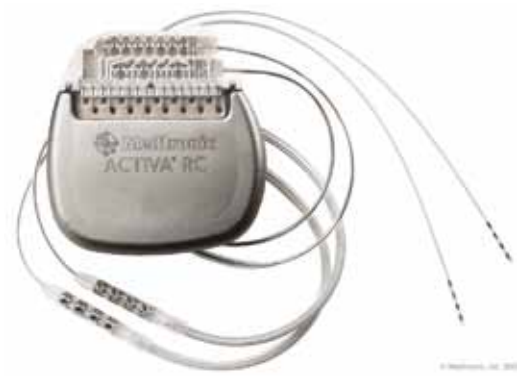

Figure 2 - Deep brain stimulator (Courtesy of Medtronic Inc., Minneapolis, MN, USA).

reported persistent seizure reduction over time in the open label period with 43% of patients having a greater than 50% reduction in seizure frequency at 13 months that increased over time, reaching 54% at 2 years, and 67% at 3 years.[8]

Safety and side effects. In the SANTE trial, stimulation of ANT was found safe. No symptomatic hemorrhages or deaths were reported. Over the course of the first year, adverse events directly related to the device included paresthesias (18.2%), implant site pain (10.9%), and implant site infections (9.1%). Stimulation related adverse effects were subjective memory impairment (6.4%), and depression (14.8%).[8] This relatively high incidence of depression is interesting; however, they mentioned that almost all of these patients had a baseline history of depression.[9]

Response neurostimulation. Response neurostimulation is a closed-loop system and an investigational treatment for MRE. The concept of RNS is to detect seizure activity early and deliver therapy to terminate the seizure. This differs from other neurostimulation strategies (VNS, DBS) that prevent the seizure by continuous delivery of current (open-loop therapy) without feedback detection from the target tissue.[48] Like DBS, FDA approval is also pending for this mode of treatment. It is the most technologically advanced therapy, and could also employ other treatment modalities such as focal cooling and targeted drug delivery to terminate the seizures.[49,50]

Therapeutic mechanism. The RNS system is designed to work through seizure detection. The seizure focus or foci must always be known and identified before implantation of the device, to place the detecting electrode and stimulating electrode near the seizure focus. The system then analyzes electrocortical potentials, and automatically delivers the targeted response stimulation to signals that are detected as electrographic seizures. This would lead to abort the evolving seizure by stopping its development and propagation.[24,51,52] This differs from VNS and DBS, which prevent the seizure by continuous delivery of current.

Suitable candidates. Response neurostimulation is indicated for patients 18 or older with MRE who are not candidates for resective surgery[7] because of medical reasons, or whose epileptogenic regions are not operable because they may be in the eloquent cortex, or who have previously undergone surgical resections,[53,54] or who have undergone VNS placement[53,55] and continue to suffer from intractable epilepsy. Because electrode implantation depends on accurate localization of the seizure foci, closed-loop systems should only be implanted if the exact epileptogenic focus or foci is known.[7]

Implantation. The implantable components of the system include a cranially implanted neurostimulator and intracranial leads (**Figure 3**). A stimulating electrode and a detection electrode are placed near the seizure focus, and the stimulation device with battery is placed in a recess in the skull bone. It can stimulate 2 different epileptogenic zones separately.[51] Programming of the device is performed using a wand attached to a computer as in VNS and DBS, with the usage of a wide range of stimulating parameters.[24]

Efficacy and outcome. Early trials for RNS have been promising.[56,57] Recently published results from

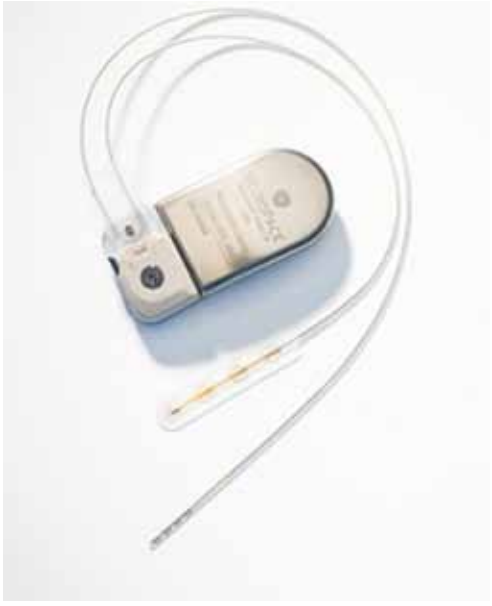

Figure 3 - Closed-loop stimulation device (Courtesy of Neuropace Inc., Mountain View, CA, USA).

the RNS pivotal trial,[7] in which 191 patients were implanted across 31 institutions, included MRE cases of age between 18-70 years. There was a 38% reduction in seizure frequency noted in the active group during the first 3 months double-blinded period, as compared with 17% in controls. This trial reported persistent seizure reduction over time with 43% at the end of the first year, and 46% at the end of the second year, and reached 53% 3 years after implantation. There was also improvement in overall quality of life. More specifically, patients reported improvement in language, memory, attention and concentration, work, driving, social function, and seizure worry.[7]

Safety and side effects. Response neurostimulation adverse events reported by year in a recent multicenter, randomized, double-blind controlled RNS pivotal trial,[7] were implant site infections (6%); implant site pain (15%); implant site swelling (8%); dysesthesia (6%); headache (20%); increased generalized seizures (5.8%); increased complex partial seizures (4.7%); depression (3.1%); and memory impairment (4.2%).[24]

Pregnancy and teratogenicity. It is safe to use VNS during pregnancy. Over the last 25 years, no case has been reported of VNS causing adverse effects during pregnancy or on the fetus.[58,59] There are also no reports of adverse effects on pregnancies with DBS and RNS.[24]

MRI compatibility with implanted neurostimulator. Vagal nerve stimulation is MRI compatible, and devices are now approved for use during MRI investigations using head coils and 1.5- to 3-tesla machines. It is recommended that the device is turned off during the procedure.[24] Deep brain stimulation is also MRI compatible;[24] no data is available for RNS.

Goal of the neurostimulation. The goal of neurostimulation therapy is the same as the goal of AED treatment of epilepsy; namely, elimination or maximal reduction of seizures without treatment related adverse effects. Neurostimulation does not change the epilepsy's natural history, so the treatment must be continued for as long as the patient is at risk for seizures.

Experience in the Kingdom of Saudi Arabia. Only VNS is being practiced in a few specialized tertiary care hospitals in the Kingdom of Saudi Arabia. In available published data, Hussein and Khan[60] shared their experience of 6 patients with intractable epilepsy that underwent VNS implantation, and reported VNS as an efficacious and safe therapy. It is advisable that more patients with refractory epilepsy are considered for referral to a comprehensive epilepsy program in the Kingdom, and more data and experience need to be shared with long-term follow-up.

In conclusion, as a third-line treatment modality, neurostimulation is facing the challenge of treating patients with refractory epilepsy. Vagal nerve stimulation, DBS with a target of ANT, and RNS all have demonstrated significant efficacy in well-designed controlled trials. Vagal nerve stimulation is approved by the FDA in the US and other countries; DBS of ANT is approved in Europe only. Response neurostimulation is currently under FDA review, having received a favorable endorsement by an advisory board in February, 2013. There are no head-to-head comparisons of these therapies to recommend one modality over the other. Based on the available evidence, it can be seen that the responses of these neurostimulation therapies are not different than those seen with new AEDs;[60] however, it can be hoped that with time, improved selection of patients, parameter optimizations, and optimal stimulation target for particular subgroups of patients can improve upon the current results. Transcranial magnetic stimulation, trigeminal nerve stimulation (TNS), hippocampal stimulation, and occipital stimulation are being currently tested as other means of neurostimulation. Among them, external TNS showed favorable results in the most recent double-blind randomized controlled trial carried out on patients with MRE,[60] and gained approval in Europe. This stimulation tool has several advantages: it is nonsurgical, consists of an external pulse generator and a self-adhesive patch that can be applied to the forehead to stimulate the ophthalmic branch of the trigeminal nerve, the device can be used at home, and 12 hours of stimulation may be affective.[61]

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