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REVIEW ARTICLE

Devices used for Treatment of Epilepsy

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ABSTRACT

Epilepsy is a group of neurological disorder of the brain that have on affects around 1-2% of the community across the world. According to the World Health Organization (WHO), epilepsy is signalizing by repeatedly spontaneous seizures, which are usually due to excessive electrical discharges in a group of nerve cells. The earlier day electroencephalogram (EEG) signals are useful tool for detection of epileptic seizures. Epileptogenesis is a slow process. After several months of initial insult, spontaneous recurrent seizures begin to appear. Epilepsy is considered to be resolved for individuals who are seizure-free for the last 10 years, with no seizure medicines for the last 5 years. Currently, used drugs available for treating epilepsy have draw backs like Epileptogenesis and other dose-related side effects. In spite of daily treatment, nearly 30% of patients continue to have convulsions and fail to provide a complete cure. Hence, there is a need for another alternative option to control the epileptic seizure and minimize the duration of seizure without taking a medicine & improving the sort of patient's life. In current scenario the devices of Vagus nerve stimulation (VNS) has become an important tool for controlling the neurological disorder like epileptic seizure. Vagus nerve stimulation devices are used for patient with refractory and drug resistant epilepsy. Various non-pharmacological treatment form preclinical to clinical for controlling seizures in epileptic patients with drug resistance, current available devices have been highlighted in this review.

Keywords: Epilepsy, electroencephalogram, Epileptogenesis, seizures, Vagus nerve.

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INTRODUCTION

Epilepsy is a group of neurological disorder characterized with recurrent episodes of seizures due to abnormal electrical activity in the brain. In epilepsy, there is predisposition to generate epileptic seizures.[1] Seizure is due to excessive abnormal neuronal activity of the brain and is associated with alterations in electrographic pattern, consciousness, sensation and behavior.[1,2.]

Epilepsy is signalizing by come and go, unprovoked seizures, affecting about 1 % of the community in entire worldwide. In spite of the creation of new drugs and anticonvulsant drug therapies over the years, about 1/3 of epileptic patients do not become seizure free and have too much resistant to AED treatment. In epilepsy patients with drug resistance, there no single drug available to cure of epilepsy rather than symptomatic relief. Therefore the non-drug therapies are very important role to minimize the duration of seizures as well as it may be cure the disease. In this review, an overview of epilepsy and available devices or drug loaded devices has given.

Epilepsy is a neurological disorder of the brain that affects around 1-2% of the population across the world. According to the World Health Organization (WHO), epilepsy is characterized by periodically spontaneous seizures, which are usually due to excessive electrical discharges in a group of brain cells. The earlier day electroencephalogram (EEG) signals are useful tool for detection of epileptic seizures.Epileptogenesis is a slow process. After several months of initial insult, spontaneous recurrent seizures begin to appear. Epilepsy is considered to be resolved for individuals who are seizure-free for the last 10 years, with no seizure medicines for the last 5 years. Currently, used drugs available for treating epilepsy have draw backs like Epileptogenesis and other dose-related side effects. Instead of daily treatment of medicine, nearly 30% of patients continue to have seizure and informal conk out to provide a complete cure. Hence, there is a need for another alternative option to control the epileptic seizure and minimize the duration of seizure without taking a medicine & improving the badge of patient's life. In current scenario the devices of Vagus nerve stimulation (VNS) has become an important tool for recover the epileptic seizure. Vagus nerve stimulation devices are used for patient with refractory and drug resistant epilepsy

The surgical approach of epilepsy has been seen in last 15 year. Surgery approaches is responsible for cure of focal epilepsy is established, but it is not frequently used in status epilepticus (SE) and other seizure types

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like atypical, typical and myoclonic. Brisk advances in surgical automation and neuroimaging are the driving forces behind these changes. In coexisting understanding of developments in epilepsy neurobiology bring us to a time when much novel surgical approach will be either in pre-clinical/ clinical trial or soon to begin application to human epileptic seizures.[3-5]

The use of various vagus nerve stimulation devices, microbeam-based and brain stimulation therapies has acquire much attention towards the epileptic patients recently. Even though some of the devices like Responsive Neurostimulator (RNS), Vagus Nerve Stimulator (VNS), are victorious, but still significant development and controlled preclinical and clinical trials are required to establish in standard clinical treatment protocols. Hence extensive range of approach to prevent seizures and need for newer therapeutic approach in epilepsy remains high.[6,11]

EPIDEMIOLOGY

The prevalence of vigorous epilepsy is 9-10 per 1000 persons in low income countries and 5-8 per 1000 persons in high income countries,[7,8] where even higher rates have been reported in rural areas.[9] Contrast in the pervasiveness rates is reliant on different danger variables and it additionally varies from one nation to other. This valor is attributed to the living conditions, inadequate prenatal care, antinatal care and various infections.[10] This was proved from a meta-analysis,[11] indicating that yearly incidence is 82 for every100 000 persons with an interquartile range (IQR) of 28-240 in low-pay and centre-pay nation and 45 per 100 000 persons with an IQR of 30-67 in high-salary nation. Despite the fact that numerous AEDs have been developed but still drug-resistant epilepsy and its associated increased risk of death and capacitating psychosocial consequences are still on.

PATHOPHYSIOLOGY

A seizure results from transient anomalous synchronization of neurons in the brain that disturbs normal patterns of neuronal communication and results in coming and going of electrical discharges in the EEG (electrographic seizure). During this period, a quick imbalance occurs between the excitatory and inhibitory of cortical neurons. In light of the degree of interruption and site of seizure origin, signs and symptoms will be fluctuated to a great extent.[11-13]

The neuronal network in the brain is profoundly interconnected and it allows for coordination of different tasks and behaviours. Any aggravation in the normal neuronal electrical impulses leads to seizures and its related comorbidities for example depression, autistic features, and learning disabilities. Headway of new innovation in neurophysiology, imaging and video recording have improved our ability to identify the correct causes behind the seizures and also identify exact epileptic foci in the brain, to establish whether seizures are focal or generalized from the start, and to define their propagation patterns.[14,15] Based on these developments in the field, site specific drug targeting can be achieved by identifying the exact location of the neurons involved in the commencement, spread, or termination of seizures.

In a current situation, the different animal models are available to study the potential therapeutic agents for the epilepsy treatment and to recognize the multiple causes leading to epilepsy.[16] Evolution of highly advanced technologies in imaging and electrophysiology can clear up the neuronal activity and its change during and after the epilepsy in brain.[17-19.]

DEVICES

Devices are used for symptomatic relief not to cure seizures and to provide a new hope and options in drug resistant epilepsy. Seizure medication helps more than 60 % of population with seizures but most of the people suffer from seizures even after medication. In such cases, alarming devices are much more helpful to prevent the symptom of epilepsy (Table 1).[20]

Vagus nerve stimulation devices play a significant role in detecting seizures, alerting family members and care givers thus helps in controlling the seizure behavior. These devices are designed to alert but not to prevent seizures and its consequences. Most of the devices are triggered depending on the repeated shaking movements as in tonic-clonic seizures and they are proved ineffective in some form of seizures like absent, focal where big movements in the body are absent. Currently three types of alerting devices are available in the market namely, mattress camera and watch devices. These devices also have their own limitations like inability to detect some type of seizures, not practical in people living alone and it do not alert other conditions like breathing problems and change in heart rate. For their success, they have to be proved scientifically and clinically in huge number of patients for various types of seizures.[6,21]

Investigational Stage Devices

External trigeminal nerve stimulation (TNS) is a rising and promising neuro-modulating non-invasive treatment for epilepsy. When contrasted with current therapies, it has its own unique advantages like lower potential of risk because there is no risk of placing electrode in the brain or risk of invasive devices; it can be delivered externally, bilaterally at reasonable expenses. The treatment begins

Table 1: Devices used in Treatment of Epilepsy

Devices	*System*
Devices for vagus nerve stimulation in brain	
Intracranial systems	
RNS	Implant device
DBS	Implant device
Extracranial systems	
RTM Stimulation	Implant device
Focal cooling and uncaging	Implant device
TNS	Implant device
TDC Stimulation	Implant device
VNS	Implant device
Devices for epileptic alerts	
BrainGateTM Neural Interface System	Sensor implant device
Accelerometer	Wearable device
Epilert	Mobile-phone-based device
Epdetect	Mobile-phone-based device
Medpage ST-2	Wearable device
NeuroPort System	Software-based multichannel sensor device
SeizAlert	Wearable device
SmartWatch Alert	Watch-based device
Devices for surgery	
Functional MRI	-
Cyber knife	-
High-resolution brain SPECT	-
Gamma knife	-
NIRS	-
Magnetoencephalography	-
SIGFRIED	-
Tractography and diffusion tensor imaging	-
Miscellaneous devices for overall epilepsy care	
Rehabilicare	Cortical stimulators and mapping systems
Safety Place Mat®	Working mats
Protective Headwear's	Wearable

RNS-responsive neurostimulation; **DBS-** Deep brain stimulation; **RTM**-repetitive transcranial magnetic stimulation;**TDS-**transcranial direct current stimulation; **TNS-**trigeminal nerve stimulation;**VNS-**vagus nerve stimulation;**NIRS**-near-infrared spectroscopy; **SIFRIED-**signal modeling for real-time identification and event detection

with a mild electrical stimulation of trigeminal nerve branches to adjust the targeted brain regions activity. At present Neurosigma has the selecting licensee for creating and assembling two embodiments of TNS.[6] (Fig. 1).

Approved Therapeutic Devices

In 1950s, Penfield and Jasper performed the ability of electrical incitement by vagus nerve stimulation devices

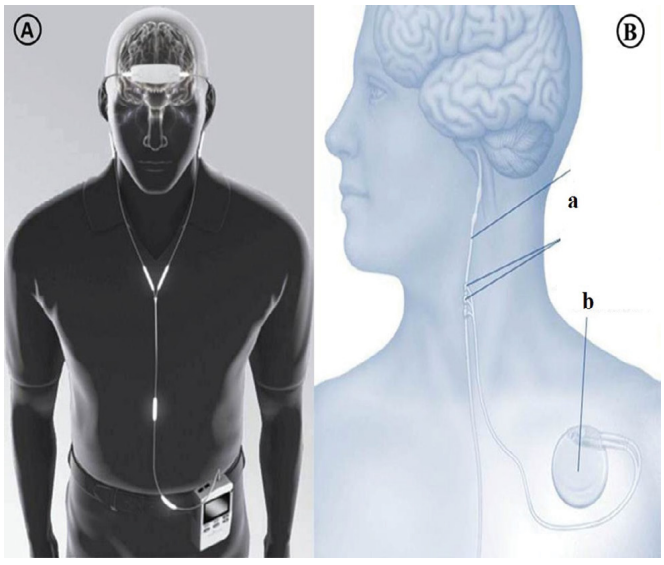

Figure 1: Investigational stage device and approved therapeutic device
A) External trigeminal nerve stimulator, B) vagus nerve stimulator a) electrodes are wrapped around the left vagus nerve in the neck b) the pulse generator is implanted under the left clavicle. Panel A image was adapted and modified from NeuroSigma, Inc. Los Angeles, CA, USA. Panel B image was adapted and modified from Cyberonics, Inc., Houston, TX, USA

and to suppress neuronal discharges on direct cortical stimulation in humans.[22] Nerve stimulation is performed by a unique device called vagus nerve stimulation (fig. 1), which also known as "pacemaker for the brain". It was affirmed for use in Europe in 1994 and by US FDA in 1997. It is an "open loop" device, meaning that there will not be any direct feedback to moderate therapy. This device is intended to control or prevent the seizures by sending mild electrical stimulations to the seizure causing areas of the brain via vagus nerve and controls the involuntary functions under it, such as heart rate thus helps in reducing the length and frequency of the seizures. These seizures preventing instruments are ideal in patients not willing or not appropriate for brain surgery and it is also considered in drug resistant epileptic patients. Vagus nerve stimulation was proved successful in reducing the seizures up to 30-40 and 10 % or fewer patients are rendered seizure-free. This device is flat, round, about a coin size. The surgical procedure includes implantation of the device under the upper chest skin and connecting its electrodes other end around the vagus nerve in the neck. The surgeon decides programmes timing and strength of the impulses of the stimulator is suitable level based for patient condition and need. Generally the stimulator will be set to give stimulations for 30 s in every 5 min during day and night. The stimulator device works on battery, which lasts for 6-10 year depending on the stimulation settings. The patient under anaesthesia, the procedure takes 50-90 min and patient can be discharged later the same day depending on the patient condition. This device

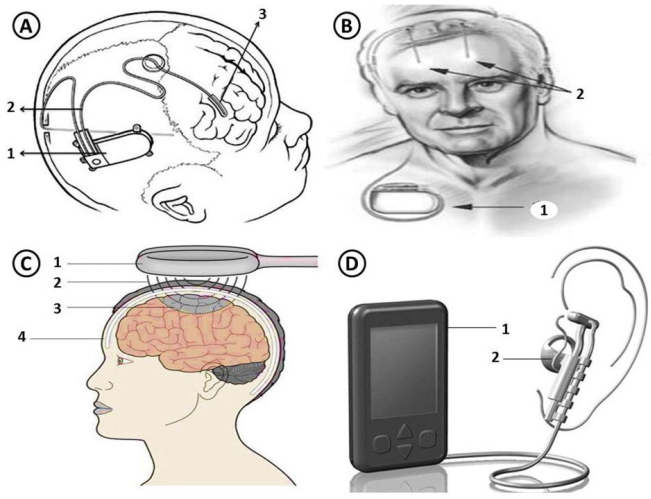

Figure 2: Approved therapeutic devices

is not a substitute for seizure medications, patient can continue the medication while using this, however if it works, then the number or dose of medications can be reduced.[6,21]

RNS (Responsive neuro-stimulation) is the first generation "closed loop" device (fig. 2). It will be embedded in skull with a strategy to directly invigorate subdural strips or electrodes on top or implanted in the brain near seizure foci to control or stop the seizures. In case of the patients is not responding to antiepileptic drug and patients with seizure foci in the brain which cannot be removed, in such cases, implanting devices are preferred. Once the device is set to particular EEG the response of the patient change accordingly on basis of individual. The implant devices help to identifying, collecting and recording the brain's EEG. Whenever the implant device detects a seizure, it transmits the electrical signal to control or disrupt the seizure activity in the brain. This device is just not a substitute to antiepileptic medication or cure for epilepsy but it helps in controlling or improving the patient condition. This devices may modify on the basis of patient response further modification in the therapy can be done for better outcome.

A. (RNS Responsive neurostimulation), (1) RNS neurostimulator (2) depth lead (3) cortical strip lead.

B: The Medtronic Kinetra device used in the SANTE (stimulation of the anterior nucleus of the thalamus in epilepsy) trial, (1) chest implanted pulse generator-implanted beneath the clavicle-one for each electrode (2) bilaterally implanted microelectrodes.

C: Transcranial magnetic stimulation device, (1) TMS Coil (2) pulsed magnetic field (3) induced electric field (4) skull.

D: Transcutaneous vagus nerve stimulation (tVNS) (1) programmable stimulation device (2) ear electrode.

TMS (Transcranial magnetic stimulation) is another method for brain incitement with certain advantage like focal treatment; non-invasive and considered as less painful, safe and direct.til now however, only case reports and preliminary clinical trial data are available, some of them have showed disappointing results.[23-26] In this method, magnetic field induced brain currents were introduced with the help of magnetic stimulator coil from a safe distance to stimulate focally and deeply in the brain tissues (fig. 2). In view of the attributes and advantages, figure-of-eight coils are widely used. The some of specific factors are successful for TMS targeting and depends on positioning of the magnetic stimulating coil over the seizure causing foci. So many other factors of stimulation parameters like frequency, duration of exposure, intensity also affects the treatment of epilepsy. The TMS devices should be used as safety measure in case of patient are suffering from brain lesions, heart diseases, pregnancy and seizure history etc. as well as patients on pump, medication or implants and untested stimulation parameters like.[6,27-29]

Transcutaneous vagus nerve stimulation (tVNS; fig. 2) is a non-invasive brain stimulation technique used to treat epilepsy by stimulating the left auricular branch of the vagus nerve at the ear conch. It is a newly developed tVNS device certified by CE (Cerbomed GmbH, Erlangen, Germany). It is an external device with a bipolar electrode attached to the skin of the left ear conch. To assess efficacy and safety of tVNS, a randomized, double-blind controlled trial was performed in patients with drug-resistant epilepsy.

The study was to demonstrate and evaluate the safety, reduction in seizure frequency, sub-group analyses and superiority of add-on therapy with tVNS (stimulation frequency 25 Hz, n=39) versus active control (1 Hz, n=37) in reducing seizure frequency from baseline to end of treatment. By the end of the treatment, mean seizure reduction was 2.9 % in the 1 Hz group and 23.4 % in the 25 Hz group with mild adverse effects. Superiority of 25 Hz tVNS over 1 Hz tVNS could not be proven in this study but efficacy data revealed results that justify further trials with larger patient numbers with longer observation periods.[30]

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