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Review Article

Medical Devices Exhibiting the Neuromodulation Technique - A Milestone for the Treatment of Migraine

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ABSTRACT

Migraine attack is increasing day-by-day due to the stressed conditions, increased heat, and improper daily routine schedules of the people. To protect the people from the chronic pain and intense migraine attacks, medical devices are introduced which are boon to the patients. Neuromodulation is the technique adapted to treat acute migraine and chronic attack. The medical devices are manufactured in such a way that performs either magnetic stimulations or electrical stimulations when initiated. Acute treatment and preventive treatment can be provided by using these medical devices. The different modes of stimulating devices, like Cefaly device, SAVI dual device, gamma core device and Nerivio medical devices have been explained. Drug free medical devices are developed to eradicate the adverse effects caused by the pharmaceutical treatment. People now-a-days are more advanced in the usage of the smart phones So devices like Nerivio which are remote or smart phone operated can be easily handled by oneself easily. The huge number of people are showing interests in its usage than the medications.

INTRODUCTION

Migraine is a type of headache characterized by repeated attacks of moderate to severe pain on one side of the head. The symptoms indicating neurological damage are seen along with the repeated headache illness known as migraine. For a year after diagnosis, it impacts about 15% of females and 6% of males. Dopamine and serotonin play important roles in the trigeminal sensory pain

pathways that are fundamental to the pathophysiology of migraines.(1)

Four phases exist in the condition of the migraine -premonitory, aura, headache, postdrome.

1. Premonitory symptoms might appear up to 24 hours before to the commencement of a migraine. Among them include unexplained mood fluctuations (either euphoric or melancholy), increased urination, excessive yawning, and food

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cravings.

2. A lot of individuals experience the phase of aura because of the bright lights or loud noises. Certain individuals are susceptible to heat waves, which can also cause weakness.

3. **Headache:** The stimulation-induced dilatation of blood vessels may be the reason of the headache' severity.

4. **Postdrome:** This is a state that precedes a person's return to health.

In recent times, besides the medications, technology also paved the way to the eradication and minimising of the intensity of the migraine to certain extent.

Neuromodulation is one of the milestones which is used in the treatment of the migraine without any existence of the drug. This would eventually lead to the decrease in the side-effects and harmful adverse reactions. The development of neuromodulation, a non-pharmacological approach for the proactive treatment and avoidance of migraines, is a significant advancement in medical research.(2) A growing method of treating headaches, it aims to reduce pain without invasive means by targeting parts of the central and peripheral nervous systems that are typically linked to the pathophysiology of headaches, such as the vagus nerve or the sphenopalatine ganglion, which is stimulated.

It is thought that stimulation of the tri-gemino-vascular system is what triggers the release of vasoactive sensory neuropeptides, especially the peptide associated to the calcium citonin gene, which intensifies the pain response.

Based on current migraine research, individuals with persistent migraine may experience serious effects, some of which may be lethal. Prolonged aura, migrainous infarction, condition migrainosus, and seizures brought on by migraines are some of these effects. Should that not be the case, migraine can also result in other side effects

such as rebound headaches, depression, vertigo, anxiety, and serotonin syndrome.

In the age of modern technology, medical research is rapidly progressing to provide complementary treatment approaches for migraine and other headache disorders in place of traditional pharmaceutical medication therapy. The most quickly expanding modality is neuromodulation, which modifies brain cell activity by applying various forms of stimulation.

Objectives:

The main objective of this process is to understand the different forms of the stimulations used for the treatment of the severe migraine headache and induce the newly developed medical devices like Nerivio easily which works effectively and does not require any sort of the drug presence in the treatment. This leads to the decrease of the abundant side effects and leads to the patient's compliance with ease.

Neuromodulation:

Neuromodulation is the process of the stimulation of the neurons and thus decreasing their effects caused during the migraine headache. The modulation of the nerves leads to the reduction of the intensity of the migraine headache utilising electrical, magnetic, or chemical stimulation, neuromodulation is the process of activating, regressing, changing, or modifying processes in the central or peripheral nervous system.(2) Because non-invasive neuromodulation techniques like non-invasive vagus nerve stimulation and single-pulse transcranial magnetic stimulation have been shown to be safe and effective, more patients and clinicians are showing interest in them. Neuromodulation, which modifies brain cell activity by applying varying forms of stimulation, is the modality that is expanding the fastest. A flexible, reversible, and non-harmful technique is what distinguishes neuromodulation. It is becoming more and more clear that this technology works safer and more



successfully than conventional drug therapy to cure migraines.

Neuromodulation and their method involved in the mechanism:

There are different neuromodulation stimulations which are involved in the mechanism of the different techniques. By electrical or magnetic pulsations, neuromodulation affects or stimulates the central or peripheral pain pathways. The goal of this technique is to reduce the pain ratings by controlling the pain systems. When pain circuits are triggered electrically or magnetically, central neurotransmitters can be altered. Using electrical or magnetic stimulations, a device called a neuromodulator modifies or modulates the activity of brain cells. While some are employed as a deterrent, others are used to halt attacks.

- 1. Transcranial Magnetic stimulation:** This is one of the neuromodulation techniques which is involved in the transcranial stimulation using the magnetic attacks. The site of action which takes place upon the stimulation is cortex. The cortex further transfers the stimulations to the thalamus and reaches Trigeminal Nerve Caudalis.
- 2. Deep Brain Stimulation:** The stimulations are likely to attack on the hypothalamus which further activates the thalamus and triggers the trigeminal nerve Caudalis.
- 3. Supraorbital Nerve Stimulation:** This type of stimulation involves the triggering of the trigeminal ganglion and activates the trigeminal nerve caudalis.
- 4. Sphenopalatine Ganglion Stimulation:** This stimulation leads to the reaching of the stimulus to the sphenopalatine ganglion that leads to the activation of the trigeminal nerve caudalis.
- 5. Occipital Nerve Stimulation:** This stimulation attacks the cervical afferents that triggers trigeminal nerve caudalis leading to the neuromodulation.

- 6. Vaginal Nerve Stimulation:** The name itself explains that it activates the vagal area and thus the trigeminal nerve caudalis is triggered by the vagal afferents.

Mode of Stimulations:

As we know that the neuromodulation techniques involve the use of the stimulation process that alternates the nerve impulses and thus this leads to the reduction of the migraine to a great extent. But the method by which the stimulator performs the stimulation also plays a major role. There are different modes of stimulation methods.

1. Electrical stimulation

2. Magnetic stimulation

- 1. Electrical stimulations:** The electrical stimulation is one of the modes of the stimulation process that the stimulator adapts to stimulate and perform the modulations that the nerves undergo. Recently, many treatments involved in the migraine are encouraging this type of the stimulations. The following are the stimulations undergone using the electrical stimulation in the management of the acute attacks of migraine are:
 - Non-invasive vagus nerve stimulation
 - External trigeminal nerve stimulation
 - Occipital and Supraorbital Nerve Stimulation
 - Transcranial direct current stimulation
 - Transcranial alternate current stimulation
- 2. Magnetic stimulation:** Magnet induced stimulation are adapted in this mode. The single-pulse transcranial magnetic stimulation and Repetitive transcranial magnetic stimulations are those which are triggered by the magnets(1). The magnetic stimulation mainly involves the neuromodulation process by producing the oscillated magnetic field. This further generates the electric field around the magnetic field and thus the electric field leads to the changes in the electrical signal and



thus the transmission of the pain signals to the nerves are deviated and thus reduces the pain.

Medical device stimulators for the migraine:

The recent advancements in the treatment of the migraine are the stimulators that alters the functions of the brain and modulates the nerve stimulation activity in the brain. Recently, Dr. Reddy's laboratories have developed the new medical device for the treatment of the migraine for the reduction of the intensity of its severity. There are certain stimulator medical devices which have created a numerous-benefits to the acute migraine attacks.

Some of the recently introduced medical devices that exhibits the neuromodulation process for the migraine are explained in this article.

Cefaly Device

The use of the Cefaly device does not require any prescription and can be used during the migraine attacks. The manufacturer of the Cefaly device is Oz Health Pharma Pty Ltd.(3) The availability of this medical device is observed in Australia without the health care provider's advice. The Cefaly device is the bipolar self-adhesive electrode consisting of the 30mm*94mm dimensions. The outcomes of this device are less when compared with that of the topiramate drug. But the patient's compliance is the major issue that is being raised in the intake of the topiramate drug. So many people are exhibiting withdrawal decisions from its usage as enormous adverse effects are being faced by the patients.

Working and its usage steps:

The mechanism involved in the working of the Cefaly device is the neuromodulation process which involves the electrical stimulation technique that exhibits the neurostimulation of the external trigeminal nerves. The Cefaly device is used in the treatment of the acute migraine. The treatment session is carried out for 60 minutes for the acute migraine attack and the 20 minutes sessions every day for the preventive treatment.



Fig 1: Cefaly device Components

- 1. Electrical impulse generation:** The electrical impulses are generated through the device but the patient needs to have clear idea about the setting of the impulse strength, frequency, and the time-period for the treatment.
- 2. Trigeminal nerve stimulation:** The Cefaly medical device consists of the electrodes which involves the interferences of the pain signals thus helps in the reduction of the pain impulses reaching to the brain.(4) Thus, the activation of the pain impulses is stopped in the brain. Neuromodulation is involved and thus the sedation effect is attained leading to the reduction of the intensity of the migraine
- 3. Neuroplasticity:** Over the time, regular stimulations could provide neuroplasticity which would further helps in the retraining of the brain.

Precautions to be followed:

- Before placing the device on the forehead, the forehead must be rinsed and cleaned with the wet cotton and dry it with the help of the cloth.
- As the device works on the principle of the electrical stimulation generations, people with the sensitivity to the electricity must avoid the usage of the device.

Principle and the mechanism involved in the treatment using Cefaly device

The Cefaly device is the first and the foremost licensed non-invasive neurostimulator which is used in the treatment of the migraine The electrical stimulations take place using this medical device leading to the transcutaneous stimulation of the

supraorbital and supratrochlear branches of the ophthalmic nerve. Generally, migraine involves the stimulation of the trigeminal nervous system and leads to the hyperexcitability of the pain. The peripheral and the central functioning of the trigeminal vascular system is reduced by the activation of the supraorbital nerve. This leads to the reduction and relief from the sensory pathways.



Fig 2: Cefaly Device

Safety and Efficacy of the Cefaly device: The device is not suitable for the patients who are prone to skin abrasions on the forehead or the allergic conditions especially acrylates. The device has exhibited the patient compliance for the acute treatment as the intensity of the impulses can be adjusted by the patient. This device mainly shows the safety and tolerability in the patient. The efficacy of the medical devices is compared with that of the placebo in the recent articles and the results were found satisfactory.

SAVI Dual Device:

SAVI Dual Device is one of the medical devices which is very easy and achieved the patient compliance for the treatment of the migraine attacks. SAVI Dual Device is one of the recently FDA cleared medical device plays a lead role in the treatment of the migraine in its early diagnosis.⁽⁵⁾ It is very appreciable that the eNeura company has developed a great device which has introduced the central neuromodulation technique to provide relief to the severely affected migraine patients. Recently this medical device is used to prevent migraine.

Working and its usage:

SAVI dual device mainly involves in the generation of the dual impulses and thus provide

the pathway for the decreasing of the intensity and the severity of the migraine attack. The SAVI dual device is in the form of a curvy box which consists of the buttons on the two ends. SAVI Dual device must be placed on the backside of the head to accomplish the treatment. The device mainly works by generating the magnetic impulses. The magnetic impulses further produce the electrical impulses leading to the disturbances in the electrical signals transformations and decrease the stimulations.



Fig 3 SAVI Dual Device

Precautions

- The medical device should not be brought in contact to the skin.
- The battery must be charged whenever required for the maintenance of the functioning of the medical device.
- Should be placed in the appropriate position for the proper treatment.

Mechanism of the treatment using SAVI Dual device:

The SAVI Dual device exhibits its actions by generating the dual actions. The device produces the magnetic impulses and are moved to the brain. These magnetic impulses further generate the electrical impulses in the brain. Thus, the signals that reaches the brain leads to the modulation and alters the hyperexcitability condition leading to the reduction of the impact and reduce the headache. The magnetic stimulation is the technique which is involved in this type of stimulator. The SAVI dual device involves the changes in the cortical neurons and thalamocortical circuits. Further leading to the oscillating magnetic field and thus electric current. Single pulse transcranial magnetic stimulation is

the mechanism involved in this treatment. The headache frequency can be diminished and the alteration of the neuronal excitability for prolonged period can be made possible by the persistent transcranial magnetic stimulation.

Usage period: The benefits are more when the device is used for 12 weeks than that of the 3 weeks, So, usage around 3 months is suggested to prevent migraine according to the severity.

Safety and Efficacy of the treatment:

The SAVI Dual device should not be used by the patients diagnosed positive with the cardiovascular diseases and disorders. The most common side-effects observed are contracting muscles, nausea, vomiting and minor dizziness.(5) Patient with the implanted pacemakers and other medical devices insertion should not use these transcranial stimulator devices as the electrical impulses generated might deviate and cause improper functioning.

C. Gamma Core Device:

Gamma core is the device which is manufactured by the electrocore company. It is one of the Non-invasive vagus nerve stimulators. The neuromodulation can be achieved by using the gamma core device. This ultimately leads to the decrease in the clusters of the headaches and relieves from the migraine pain and its intensity. The handling of this device is very easy and the maintenance of the patient's compliance is also ultimately achieved. It is the first non-invasive vagus nerve stimulator.



Fig 4- gamma Core device

Working of the gamma core:

The device is placed on the skin near the neck for the electrical stimulation of the vagus nerve. The electrical stimulations lead to the neuromodulation & also prevents the pain signals reaching the brain eventually. The randomised PRESTO study claimed that the relief from the migraine attack can be procured between 30min to 60 min the post migraine attack. The device is the portable electrical stimulator. (4)

Mechanism involved for the migraine treatment:

The device is targeted to permit the release of the electrical current signals to the tenth cranial nerve of the cervical branch. The electric stimulation is achieved to reverse the sensitization in the central nerves and glutamate levels are decreased which are the ultimate reason for the cause of the chronic headache. (6)The vagus nerve stimulation suppresses the activity of the limbic system, thalamus, dorsal pons etc.,

Safety and Tolerability:

The device is found to be very effective in the management of the migraine and the chronic conditions of the cluster headache. According to the previous surveys conducted, the outcomes were found satisfactory and many patients showed the compliance with the usage of the device. The vagus nerve stimulations are received transcutaneous and suppress the pain by the neuromodulation process due to the electrical stimulations. The use of this device is contraindicated in the patients with the implantable devices in their body because the electrical impulses might disturb their functioning.

Cautions

- Those patients with the positive history of the carotid atherosclerosis and cervical vagotomy should not adapt these devices.
- One must discontinue its usage if prone to any skin irritation at the site of the treatment.

D. Nerivio Device:

The first and only gadget authorised by the USFDA to employ Remote Electrical Neuromodulation (REN) for migraine treatment and prevention is called Nerivio®. Dr. Reddy's Laboratories launched Nerivio, a wearable therapeutic device for migraine treatment. The Nerivio device is the first and the foremost USFDA approved remote based electronic neuromodulation (REN) device which is placed on the arm for the initiation of treatment on the migraine attacks.(7)

Working of the Nerivio device:

One can wear the gadget on your upper arm. When treating a migraine acutely, it must be taken within 60 minutes of the start of the headache, or every other day to avoid migraines. Applying the device to the upper arm over dry, healthy skin that has normal feeling is the sole appropriate use for it. It should not be done over metallic implants or near malignant tumours. The gadget must be thrown away and replaced with a new one after 18 sessions. The device's intensity settings may be adjusted via an app. The intuitive Nerivio app has built-in features including an interactive migraine diary to record symptoms, monitor reactions, and share informative insights.

Additionally, the app has an interactive GIER (guided, imagery, education, and relaxation) programme that considerably raises response rates when utilised in conjunction with Nerivio®.(8)

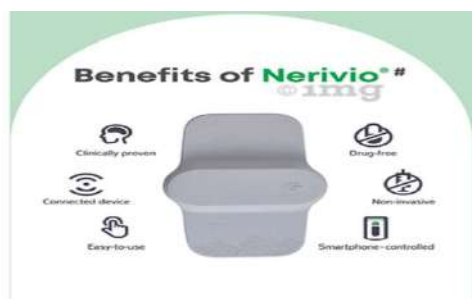


Fig 5: Nerivio device

Mechanism involved:

This gadget stimulates nerve endings using the Remote Electrical Neuromodulation (REN) mechanism to selectively trigger conditioned pain modulation. This triggers the brainstem's natural pain-relieving mechanism, which has the effect of globally inhibiting pain and affecting the head's primary source of migraine discomfort. (9)Electrical pulses are sent by the apparatus. By raising it to the maximum level that feels powerful but pleasant and painless, the user must adjust the intensity level of the treatment. Initially you could have a powerful feeling, but after a few seconds, it usually subsides to a tolerable level. Reducing the intensity is advised if the sensation is unpleasant or uncomfortable. Additional symptoms that may appear include a brief feeling of warmth, localized tingling, arm soreness, numbness, or redness.

Precautions for use:

Uncontrolled epileptics and individuals with active implanted medical devices, such as pacemakers, hearing aids, or any implanted electronic device, should not use this device.

S. No	Name of the device	Manufacturer	Mode of action
1	Cefaly device	Oz Health Pharma Pty Ltd	Electrical Stimulation
2	SAVI Dual Device	eNeura company	Magnetic Stimulation
3	Gamma Core device	Electro core company	Electrical Stimulation
4	Nerivio device	Dr. Reddy's Laboratories	Remote Electrical Neuromodulation (REN)

Table: 1 Medical Devices outline data

CONCLUSION:

Migraine is the most commonly occurring problem in the recent days in many people including teens

due to the increased stress and improper diet intake of the food in their daily routine. Many drugs are available in the market to treat acute and chronic attacks of the migraine. But all these medications are being ended up by the cause of the severe side-effects and non-compliance of its use by the patients. So, the development of the drug-free medical devices for the treatment of the chronic pain of the migraine has paved the way for the comfortable treatment conditions to the patients. Surveys are conducted to determine the outcomes of these medical devices and shown that the medical devices produced huge benefits and the ultimate relief to the patients than that of the pharmaceutical treatment.

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