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TABLE OF CONTENTS

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Editorial

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Mobile Stroke Unit (MSU): The Future of Acute Stroke Treatment?

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Time is the key factor in brain survivability in acute stroke treatment.[1] The therapeutic effects of intravenous recombinant tissue Plasminogen Activator (IV rtPA) are highly dependent on time.[1-3] Stroke patients presenting within the first 60 minutes, or the golden hour, are the most likely to benefit from recanalization therapy.[1-3] Thus, making rapid clinical and imaging evaluation of stroke patients of upmost importance and very difficult to complete within the golden hour time window. Based on Get with the Guidelines-Stroke Program (April 2003 to October 2009), less than one-third of patients treated with IV rtPA have door-to-needle times of less than 60 minutes.[4]

However, the delivery of care to a stroke victim is complex and involves pre-hospital and in-hospital stages. Once the patient arrives in a hospital, the recommended door-to-needle time is less than 60 mins.[5] Despite combined efforts to streamline procedures in hospitals to provide treatment as soon as possible, most places are challenged to stay within this time window.[4,6] In fact, most patients are still treated with considerable delay and very few of them receive intravenous tissue Plasminogen Activator (tPA) within 90 mins after symptom onset.[6] While the number needed to treat in order to achieve a modified Rankin Scale (mRS) of 0-1 is only 4.[5] when treatment is provided within 90 mins, it raises to 9 between 90 and 180 mins and exceeds 14 by 4.5 h.[2]

The majority of the delay in treating these patients is related to prehospital delay. Rapid triage of such patients could lead to faster treatment with acute therapies such as IV rtPA. To increase the number of patients treated within the golden hour, Mobile Stroke Units (MSUs) have emerged as the potential mitigation of this problem and as the future of acute stroke treatment. Currently, MSUs have emerged in Germany as well in the Unites States in Houston and Cleveland.

The MSU concept offers a remedy to the "time" dilemma in acute stroke management. Stroke patients can be triaged at the scene and taken directly to comprehensive stroke centers without delay and bypassing potential delays in subsequent transfers. Acute stroke patients could also receive prompt imaging in the Mobile Stroke Unit, which in turn would lead to faster triaging of patients and their care. However, the MSU is more than just a mobile CT scanner; it also provides a platform for point of care laboratory testing, telemedicine, and acute management of stroke including the prompt administration of systemic thrombolysis.

This strategy was first proposed in Germany in 2003[7] and shown to be feasible in 2010.[8] In 2012, Walter et al reported findings from a single-center prospective randomized trial involving 100 patients in Saarland, Germany.[9] They demonstrated a 50% reduction in the delay to a therapy decision regarding IV tPA administration. The median alarm to-therapy decision time of 35 minutes and the symptom-onset-to-needle time of 72 min were shorter than all other reported time limits for stroke management. In 2014, Ebinger et al reported on a similar model implemented in Berlin, Germany.[10] The study included 6182 patients who were randomized to weeks with and without availability of the mobile stroke ambulance. Compared to control

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weeks, there was a reduction by 25 minutes from mean-alarm to treatment time. In addition, the rate of tPA administration was 33% during MSTU weeks, compared to 21% during control weeks.

MSUs could also allow for patients with suspected large-vessel occlusion to be specifically triaged to specialized stroke centers that offer endovascular treatment.[11] Most recently the Cleveland MSU group was able to demonstrate this concept and the effectiveness in the MSU in the rapid triage of patients with Acute Ischemic Stroke (AIS) from large vessel occlusions to a facility with interventional capabilities thereby saving precious time spent in inter hospital transfers.[12] In their study they were able to show that the time from door to groin puncture, and the first picture to groin puncture was shorter by almost one-half in the Mobile stroke treatment units (MSTUs) group when compared to Emergency Medical Systems (EMS)/private transport. Moreover, the MSU could allow for organization of further specialized treatments and etiology-specific blood pressure management already in the pre-hospital phase of stroke management.[8,13-14] The latter could be specifically clinically relevant because there are indications that differential adjustment of blood pressure can be beneficial for patients with ischemic stroke (tolerating higher blood pressure values) or hemorrhagic stroke (reducing elevated blood pressure).[11]

In addition, the implementation of the MSU has made the management of hemorrhagic stroke faster, with earlier blood pressure reduction based on the most recent guidelines.[15] Having intravenous antihypertensive medications on board the MSU with experienced medical personnel familiar with their use and titration makes the hyper acute management of hemorrhagic stroke potentially more effective. Because hemorrhage enlargement occurs more frequently early in the course of intra cerebral hemorrhage,[16-18] the MSU might be a useful venue for testing out new therapies to limit bleeding. The Cleveland MSU group recently applied this principle, and they were able to initiate warfarin reversal within 57 minutes of EMS dispatch, with an MSTU door-to-needle time of 40 minutes.[19] This new treatment paradigm combining a fast-acting reversal agent with remote physician evaluation, on-site imaging, and laboratory testing for the first time affords ultra early reversal of warfarin effect. If earlier time to antihypertensive or coagulopathy reversal treatments benefits in preventing hematoma expansion, the MSU might have an important role in delivering and showing the efficacy of early hemorrhagic stroke treatment.

The next step needed is to address the generalizability of such units. Each state, municipality, and collaborating EMS agency might have different requirements for ensuring accountability, licensing, radiation safety, and insurance. The reality is that emergency medical systems (EMS) Germany as in rural Ocala, Florida. How much time can be saved by use of MSUs in the United States where traffic patterns, distances, market forces, and local regulations differ from Germany, is also likely to be location-specific and differ between urban and rural areas. Furthermore, most cities in Germany have a highly developed emergency care system with specifically trained doctors on ambulances,[20] which is not the case in the United States. Implementing MSUs across various cities in the Unites States would require many MSUs, cooperation of various different kinds of EMS systems/personal, and exceptional coordination within the system to overcome logistical issues. Furthermore, deployment of an MSU in a rural or ex-urban area would require different organization.

The cost-effectiveness of the MSU also still needs to be studied and compared with other strategies of remotely triaging stroke patients including the use of telestroke alone.[21] Financial sustainability will be a major issue and the biggest barriers to this ground-breaking approach in acute stroke treatment will be logistical and financial. The advantages of the MSU have to be weighed against the costs of the project, including expenses for investments, staff, and consumables. Other issues, besides staffing, that will determine net costs include the design of the MSU and reimbursement for drugs, transport, and physician services. Judicious attention to cost control will be needed when making the case for MSU coverage by healthcare payers. A health economic analysis needs to be carried out as part of the MSU trials.

In summary, logistical and financial barriers remained to be solved. In addition, more clinical studies are needed to explore the long-term clinical outcomes in patients. Even in light of these obstacles, MSUs have the potential to be the future of acute stroke treatment.

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ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-3-e005

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Editorial

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Neuromodulation and Non-Pharmacological Treatment of Migraine

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Migraine is a chronic brain disorder that is believed to be due to dysfunction of the brain and brainstem that result in dysmodulation of sensory processing of the head and vascular tone. The exact pathomechanism of migraine is not known but some genes including mutations in the sodium and calcium channels and Na^+/K^+ pump have been implicated in migraine with aura.[1-8]

Several drugs are currently used in the acute and preventive treatment of migraine. These include the non-steroidal anti-inflammatory drugs, the triptan family, anti-epileptic drugs, beta-blockers, calcium channel blockers, steroids, and recently antibodies against calcitonin gene-related peptide (CGRP) or its receptor among other drugs.[5,9] Some other drugs are under investigation and the CGRP receptor antagonists (the gepant family drugs), were discontinued although other drugs in this category are still under investigation.[10-16] However, there are some medically intractable headaches or unsatisfactory patient management or medications are poorly tolerated, therefore, additional treatment options might be helpful.

A number of nonpharmacological methods such as education, reassurance, avoiding the triggers of migraine, and physical and/or complementary medicine when appropriate, have also been recommended in the treatment of migraine and other headaches.[17,18] Dietary modifications and lifestyle changes have also been suggested.[19] Other methods such as physical therapy with relaxation and thermal biofeedback have also been used in the treatment of migraine.[20,21]

A recent meta-analysis of biofeedback in treatment of pediatric migraine shows some effectiveness but more research is needed.[22]

A recent pilot randomized controlled trial shows that frontal electromyography biofeed-back added to traditional pharmacological therapy is promising in the prophylactic treatment of medication overuse headache by reducing the frequency of headache and analgesic intake.[23]

Other nonpharmacological approaches such as behavioral, and body/mind treatment of headache were reported to be effective[24] and an 8-week mindfulness-based stress reduction method by meditation in adult migraine patients shows some beneficial effects[25] although more studies are needed.

Other methods such as massage therapy of the neck and upper thoracic region[26-28] or acupuncture studies have shown some efficacy in the treatment of chronic headache[29-31] but more research is necessary.[32]

The nonpharmacological treatment options of migraine warrants a review paper by itself to understand current opinion in this area. However, our focus in this issue will be on neuromodulation by electrical stimulation of peripheral and central nerves/neurons that are currently being used in clinical studies for the acute and preventive treatment of migraine.[33]

Currently, electrical stimulation of various nerves is being used through a number of

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invasive and non-invasive methods in clinical studies for the acute and preventive treatment of chronic migraine particularly on those patients with medically intractable headaches, non-responders to medication, or when medication is poorly tolerated.

For the invasive procedures the stimulating devices are implanted subcutaneously by surgery. They are powered by implantable batteries or controlled wirelessly. The noninvasive devices are applied on the skin close to the nerve and are also self-administered by the patient.[34]

Some of the neurostimulation methods used in clinical studies include the invasive electrical stimulation of greater occipital nerve and the sphenopalatine ganglion, and non-invasive electrical stimulation of supraorbital nerve or vagus nerve, and single-pulse transcranial magnetic stimulation.

Electrical stimulation of greater occipital nerve is an invasive method that has been used by some investigators in clinical studies in recent years to treat chronic migraine. Among these, two studies were prominent: the ONSTIM feasibility study was one of the first multicenter, randomized, blinded studies aimed for the preventive treatment of chronic migraine.[35] They used Occipital Nerve Stimulation (ONS) by means of a pulse generator device implanted subcutaneously superficial to the fascia and muscle layer at the level of C1.[35] The study had 110 participants and they found 39% 3-month responders with 50% or more reduction in the number of headache days per month in the adjustable stimulation group compared to 6% 3-month responders rate in the preset stimulation group and 0% in medical management group.[35]

Similarly, another large-scale, multicenter, investigation with ONS performed on 105 chronic migraine patients and 52 with sham stimulation showed only a significant difference in the percentage of patients who had 30% pain reduction (decrease in mean daily visual analog scale scores by 12 weeks) following the procedure, since the difference between the active stimulated and the sham stimulated group was not significant at their primary end point designated for ≥50% pain reduction.[36]

Other ONS studies are not mentioned here. In spite of some success reports in ONS, results are diverse and more clinical studies are needed to fully recommend it for the preventive treatment of migraine.[37]

Electrical stimulation of the Sphenopalatine Ganglion (SPG) is also an invasive method. It has been used in one clinical study for ≤60 minutes in 10 patients with refractory migraine and relieved the pain in 50% of the patients. The ganglion was accessed by a needle through infrazygomatic trans coronoid approach under fluoroscopy and then stimulated by means of a Medtronic 3057 test stimulation lead after induction of migraine.[38] Clinical trials (NCT01540799, and NCT02510742, https://clinicaltrials.gov) might shed light into the effect of the electrical stimulation of the SPG in migraine patients. Although currently, the procedure is not yet recommended for migraine treatment,[37] SPG innervation and function may correspond to some autonomic symptoms seen in migraine and cluster headaches. Therefore, this area of clinical research is very interesting and may add more insight in our understanding of the pathomechanism and treatment of headache.

Another invasive study using high cervical spinal cord stimulation with an implanted device in 17 chronic migraine patients for 15 months (with a range of 2-48 months following implantation) shows some positive outcomes.[39] In that study, the mean pain intensity decreased by 60%, where 71% of patients had 50% or more reduction of pain but more studies are warranted.[39]

Another similar invasive study delivering 10 kHz spinal cord stimulation in 14 successfully implanted patients with chronic refractory migraine who had the implant for 6 months shows that seven (50%) of the 14 subjects had >30% reduction in headache days and that the procedure did not cause paresthesia, one of the problems often encountered in nerve stimulation.[40]

There are a number of non-invasive electrical stimulation procedures such as transcutaneous vagal nerve stimulation,[41-46] the transcutaneous electrical stimulation of supraorbital nerve[47-49] and single-pulse transcranial magnetic stimulation[50-52] that have shown some efficacy in the acute and preventive treatment of migraine but more studies are necessary. Among these, vagal nerve stimulation is promising and more studies are necessary to understand the mechanism of pain relief which might to be due to modulatory effect of vagal afferent terminating in the brain stem trigeminal nucleus and brain centers.[53,54]

The mechanism of pain relief by electrical stimulation of the nerves might be the modulation of neurotransmitters and neuropeptides release in the central nervous system and closing the gate of pain and brain centers involved in pain modulation.[55,56]

In conclusion, neuromodulation studies show some efficacy in the acute and preventive treatment of migraine. The results of vagal nerve stimulation are promising and sphenopalatine ganglion stimulation studies might be very interesting and may shed light into our understanding of pathomechanism of headache. More clinical studies using neurostimulation are needed to see their

efficacy, long-term effects and side effect, tolerability and convenience in patients.

Currently, the European Headache Federation consensus statement on clinical use of neuromodulation in headache recommends the use of neurostimulation devices in patients with medically intractable syndromes taking part in valid investigations or those procedures that have proven effective in controlled studies with side effects that are acceptable.[57]

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CONFLICTS OF INTEREST

There is no conflicts of interest.

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Short Communication

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Carotid Artery Atheromatosis Detected With Doppler Ultrasonography In Patients With Normal Tension Glaucoma

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ABSTRACT

Normal Tension Glaucoma (NTG) is an optic progressive neuropathy with intraocular pressures <21 mmHg. It is a disease with multifactorial proposed pathogenetic mechanisms, one of them being intracranial or systemic vasculopathy. Seventy-seven percent of patients with NTG showed some degree of carotid atheromatosis when scanned with carotid US-Doppler. Six percent of patients showed significant burden to carotid blood flow.

KEYWORDS: Normal tension glaucoma; Carotid artery atheromatosis; US-Doppler.

INTRODUCTION

Glaucoma is the leading cause of blindness in the world, affecting approximately 60 million people.[1] In this disease there is a progressive loss of retinal ganglion cells and their axons associating remodeling of the Optic Nerve Head (ONH). Left without control this disease produces progressive visual field deterioration in the area of anatomical ONH and Retinal Nerve Fiber Layer (RNFL). It is a multifactorial disease, with pathogenic mechanisms not fully understood. Intraocular pressure (IOP) is the most important factor in the development and progression of glaucoma, but reducing IOP does not mean ending of the disease. Some patients suffer from glaucoma progression despite low IOP.[2]

Normal Tension Glaucoma (NTG) is an optic progressive neuropathy with IOP lower than 21 mmHG, with no known cause. Diagnosis is established once other optic neuropathies have been excluded. One of the proposed pathogenetic mechanisms in the development of the disease is the reduction in ocular and cerebral blood flow. It could be a manifestation of either intracranial or systemic vasculopathy rather than an isolated orbitary process. Coexistent micro- and macro-vascular disorders have been observed in NTG patients. The impact of these alterations and the relationship between them are in part unknown.[3]

MATERIALS AND METHODS

Series of 61 patients, 18 males and 43 females with ages between 39-88 years (mean age: 63 years) referred for Carotid-Doppler US with clinical diagnosis of NTG.

Common Carotid Artery (CCA) and Internal Carotid Artery (ICA) ultrasound scan was performed using a Siemens Antares Sonoline (Elangen, Germany) platform with a V10-5 lineal probe, insonation frequency 4.71 MHz, dynamic range 55 dB and PRF set in the 3000-4000 Hz range. The scan is practiced with the patient supine, the head slightly extended with a contralateral rotation of 15-20 degrees. One of the patients was scanned sitting in her wheel chair, with the rest of the exam keeping the same parameters.

The internal carotid stenosis degree was set using criteria established by the Society of

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Radiologists in Ultrasound Consensus Conference.[4] As patients were examined with a usual clinical diagnostic method informed consent was not considered necessary.

RESULTS

Atheromatous plaques were present in 47 patients (77%). Twenty-nine patients (41%) had calcific plaques and 18 patients (29%), fibro-lipidic plaques. Two patients (3%) had complete occlusion of one of their ICA. Two patients (3%) presented significant stenosis (higher than 70%) of at least one of the ICA; 7 patients (11%) presented carotid luminal reduction between 50-69%; 50 patients (82%) had 0-49% reduction of ICA diameters.

DISCUSSION

It has been estimated that 15-25% of patients with Primary Open Angle Glaucoma (POAG) suffer from NTG. In the Baltimore Eye Study, 50% of patients with glaucomatous ONH and VF changes had IOP lower than 21 mmHG in one visit and 33% had IOP lower than 21 mmHg in two determinations. This finding is important because it influences treatment of this group of patients.[5,6]

Glaucoma patients show loss of retinal ganglion cells with thinning of the retinal nerve fiber layer, deformity of optic nerve and of the head of optic nerve. Degenerative changes in lateral geniculate nucleus and in central visual pathways have been associated. RM scans showed higher prevalence of white matter lesions and ischemic changes secondary to small vessel disease in NTG patients when compared with control groups. These findings, along with coexistence of vascular risk factors in patients with optical nerve glaucomatous lesion suggest ischemia as an important factor in the progression of glaucoma.[7]

Patients with recently diagnosed NTG present signs of subclinical vascular abnormalities at micro- and macro-vascular levels, making necessary to consider circulation system pathologies in the development and progression of this disease.[3]

Patients with suspected NTG comprised about 10% of patients referred to our Radiology Department for a US-Doppler carotid scan. An important part of them (77%) presented atheromatous lesions in carotid artery walls. About 6% of patients had significant carotid artery permeability impairment, proportion slightly greater than that published in other studies.[8] In our opinion these data make necessary screening for carotid artery lesions in patients with NTG.

CONFLICTS OF INTEREST: None.

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Clinical Data Associated With the Therapeutic Response to Glatiramer Acetate in Multiple Sclerosis Patients

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ABSTRACT

Background: The increasing appearance of new drugs is making more difficult the choice of treatment in multiple sclerosis. According to different criteria, between 20 to 50% of the patients with multiple sclerosis (MS) treated with the classical disease modify treatments (DMT) will have an incomplete response and will need a change for more aggressive therapies. For this reason it is of great importance to improve the selection process in these patients to avoid treatment failures, side-effects and unnecessary risks. The utility of clinical and epidemiological data for the prediction of the therapeutic response to the different MS treatments, and particularly to glatiramer acetate (GA), is insufficient and contradictory.
Objective: To develop a predictive model of clinical data associated with the clinical response to GA.
Methods: Observational retrospective study by reviewing medical charts from October/2002 to February/2012. Data analysis was conducted from February/2014 to February/2015. Inclusion criteria: Relapsing-remitting multiple sclerosis (RRMS McDonald 2010) with ≥1 relapses in the previous 2 years, and ≥2 years of treatment with GA. All the patients included in this study were treated with GA 20 mg injected subcutaneously once daily as the newer formulation of GA 40 mg 3 times weekly was not approved at the time of the study. Definitions: Responders: ≤1 relapse and no disability progression; Non-responders: ≥2 relapses and/or disability progression. Disability progression: EDSS increase ≥1.5 points if basal EDSS=0; increase ≥1 if basal EDSS=1-5; increase ≥0.5 if basal EDSS ≥5.5. Statistical analysis: logistic regression. Association variable: odds ratio.
Results: Two hundred and four subjects included. Responders: 137 (67.5%). Number of relapses in the 2 years before GA onset was associated with a worse clinical response (odds ratio (OR): 1.4; IC 95%: 1.12-1.74%). Accuracy of this model (AUC: 63.5%; IC 95%: 56.2-70.7%); Diagnostic parameters: Sensitivity: 40%; specificity: 79.8%, positive predictive value: 78.6; negative predictive value: 41.7.
Conclusions: GA was associated with a better response in Relapsing-remitting multiple sclerosis (RRMS) patients with low-moderate disease activity. This model could be improved incorporating serological, genetic and imaging data.

KEYWORDS: Multiple sclerosis; Glatiramer acetate; Clinical response; Predictive factors.

ABBREVIATIONS: MS: Multiple Sclerosis; CNS: Central Nervous System; DMT: Disease Modify Treatments; GA: Glatiramer Acetate; MBP: Myelin Basic Protein.

INTRODUCTION

Multiple sclerosis (MS) is a demyelinating and neurodegenerative disease of the central nervous system (CNS) that affects a high number of patients in the western world and represents the 2nd cause of disability in young people of these countries.[1,2]

Its causes are not completely understood, but it is accepted that it has a multifactorial origin, with environmental and genetic factors playing a role and then autoimmune and neurodegenerative mechanisms against the myelin sheath.[3]

Over the last years, we are witnessing a great progress in the treatment of multiple sclerosis (MS). Currently there are 10 therapies approved for this disease, and this number is going to increase in the near future with other several drugs in the last stages of their clinical trials, making more difficult to choose the best treatment for each individual patient.

According to different criteria, between 20 to 50% of the patients with MS treated with the classical disease modify treatments (DMT) will have an incomplete response,[4-6] and will need a change in their therapy. In this scenario, it is becoming more important to develop tools that allow an earlier prediction of the clinical response, and improve the therapeutic election, by avoiding therapeutic failures of first-line treatments or unnecessary risks from more aggressive drugs.

The glatiramer acetate (GA) is a classic immunomodulator which consists of a mix of oligopeptides of 4 amino-acids that resembles the myelin basic protein (MBP),[7,8] and with a well documented efficacy and tolerability both at short and long-term.[9-16] Recently it has been approved a new formulation of 40 mg which is given with subcutaneous injections 3-times weekly, instead the previous 20 mg once-daily, with the same efficacy and safety profile.[17,18]

The objective of this study is to build a predictive model of clinical data associated with the clinical response to GA, to improve the treatment selection in patients with MS.

MATERIAL AND METHODS

Design and Study Population

Retrospective and observational study by reviewing the medical charts of the patients attending to the demyelinating diseases unit of the Clinico San Carlos Hospital (HCSC) (Madrid, Spain), from October, 2002 to February, 2012. Data analysis was conducted from February, 2014 to February, 2015.

We included all the patients with the diagnosis of relapsing-remitting multiple sclerosis (RRMS),[19] with at least 1 relapse in the last 2 years before the initiation of GA, and who had received treatment with GA for a minimum of 2 years. Those patients who suspended GA before 2 years of therapy due to early clinical failure were also included. All the patients included in this study were treated with GA 20 mg injected subcutaneously once daily as the newer formulation of GA 40 mg 3 times weekly was not approved at the time of the study.

We analyzed the variables: sex, age at onset of MS, previous treatments, age at onset of GA, number of relapses in the 2 years before GA, number of relapses during the study, basal expanded disability status scale (EDSS), and EDSS every 6 months.

The patients gave their written consent to participate in this study. The research fulfilled with all the Helsinki declaration requirements, and was approved by the ethics committee of the HCSC. The results of the study are completely confidential complying with all the legal steps established in the 1999 Spanish data protection law.

Definitions

We considered responder (R) those patients with no more than 1 relapse and without disability progression (DP), and non-responder (NR) those patients with ≥2 relapses and/or DP. Patients who withdrew GA before 2 years due to early clinical failure were also classified as NR.

We defined DP as an increase in the EDSS of ≥1.5 points if basal EDSS=0; ≥1 if basal EDSS=1-5; and ≥0.5 if basal EDSS ≥5.5.

These criteria were chosen because their wide use in the majority of other studies, and to optimize the detection of clinically significant associations, and therefore their applicability in the routine daily practice.[10,11,20,21]

Statistics

The statistical analysis was done using the IBM© SPSS Statistics® software for windows, version 19.

The study of the association between the clinical data and the therapeutic response to GA was done with binary logistic regression. We used the odds ratio (OR) as the association variable.

The calibration of the model was studied using the Hosmer and Lemeshow test for goodness of fit.

The accuracy of the model was calculated using the area under the curve (AUC) with receiver operating characteristic (ROC) models. The sensitivity (SE) and specificity (SP) were estimated with the regression model. The positive predictive

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value (PPV) and the negative predictive value (NPV) were estimated using the Baye's theorem with the macro! DT for IBM© SPSS® Statistics software.[22]

The statistical significance was established at $p<0.05$ for all of the statistical tests.

RESULTS

Two hundred and four patients were included. One hundred and seventy eight completed at least 2 years of GA, and 26 were included as early treatment failure.

There were 139 women (68%) and 65 men (32%). The mean age at diagnosis of MS was 30.8 years (SD±9.01), and the mean age at onset of GA was 35.9 years (SD±9.2). The mean basal EDSS was 1.8 (SD±1.03) and the mean number of relapses in the previous 2 years was 2.1 (SD± 1.4). One hundred and fifty six (76.5%) out of the 204 patients were using GA as their 1st therapeutic option, and 23.5% (48) as second line treatment after immunosuppressants or interferon beta (IFN-b) failure.

There were 137 responders. This represented a proportion of response of 67.5% (IC 95%: 61-74%).

Number of relapses in the previous 2 years before the initiation of GA was associated with the probability of response to GA. The rest of variables were not statistically associated (Table 1).

Each relapse in the previous 2 years before GA onset increased the risk for lack of response to GA in 1.4 (IC 95%: 1.12-1.74; $p=0.003$). Age of onset of MS showed a trend to a better response in older patients, but without achieving statistical significance (OR: 0.96; $p=0.051$). This could be due to less aggressive disease in older patients as inflammatory component of MS and relapses tend to decrease with time.

The calibration of the model was excellent without statistically significant differences between the predictions and the real results (chi-square=1.64, $p=0.89$).

The accuracy of the model was moderate, with a proportion of correct predictions of 64.7% (IC 95%: 55-74.5%). Using ROC curves to determine the best threshold to classify responders, we chose a probability of response of ≥70%. This value yielded a low sensitivity (42.7%) but with a good specificity (79.2%). With the percentage of response previously obtained in our study and these diagnostic values, we would have the following positive and negative predictive values (Table 2).

Combining the number of relapses and the basal-EDSS in a prognostic table, the probability of response to GA would be the following (Table 3).

DISCUSSION

The utility of clinical and epidemiological data for the prediction of the therapeutic response to the different MS treatments, and particularly to GA, is insufficient and contradictory.

On the one hand, the first clinical trials of GA showed a trend to fewer relapses in those patients with lower basal EDSS,[9-11] and a meta-analysis of the 3 pivotal trials of GA found that the starting EDSS and the number of attacks during the last 2 years were predictive factors of relapses.[23] In the same way, some observational studies did also describe such predictive factors. One of these researches, conducted on 272 patients to assess the

Variable	OR for GA failure	CI 95%	*p*
Sex	0,97	0,54-1,74	*p*=0,92
Age at MS onset	0,96	0,93-1	*p*=0,051
Age at GA onset	1,02	0,97-1,08	*p*=0,38
GA 1st line VS 2nd line	1,23	0,66-2,54	*p*=0,45
Basal EDSS	1,05	0,79-1,39	*p*=0,73
Nº relapses last year	1,19	0,77-1,84	*p*=0,43
Nº relapses 2 last years	1,33	1,09-1,63	*p*=0,003*

GA: Glatiramer acetate; MS: Multiple sclerosis; EDSS: Expanded disability status scale; OR: Odds Ratio; CI: Confidence interval; *p*: *p* value.

Table 1: Association between clinical variables and clinical response to glatiramer acetate.

Hypothetical prevalence	Positive predictive value	Negative predictive value
58%	73,9%	50%
65%	79,2%	42,7%
70%	82,7%	37,2%

Table 2: Diagnostic values of the logistic regression model.

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Basal EDSS	Nº of relapses in the last 2 years					
	1	2	3	4	5	6
0	82,1%	77,1%	71,2%	64,5%	57,2%	49,5%
1	78,6%	73,1%	66,5%	59,4%	51,8%	46,1%
1,5	76,8%	70,8%	64,1%	56,7%	49,1%	41,5%
2	74,8%	68,5%	61,6%	54,1%	46,4%	38,9%
2,5	72,7%	66,2%	59%	51,4%	43,7%	36,3%
3	70,5%	63,7%	56,3%	48,6%	41,1%	33,8%
3,5	68,2%	61,1%	53,6%	45,9%	38,3%	31,5%
4	65,8%	58,5%	50,9%	43,3%	35,9%	29,2%
4,5	63,3%	55,9%	48,2%	40,6%	33,5%	27%
5	60,7%	53,2%	45,5%	38%	31,1%	24,9%
5,5	58,2%	50,5%	42,8%	35,5%	28,8%	22,9%
6	55,5%	47,8%	40,2%	33,1%	26,7%	21,1%

Table 3: Probability of response to glatiramer acetate in relapsing remitting multiple sclerosis patients using the number of relapses in the last 2 years and the basal-EDSS as predictors.

response to IFN-b and GA, found that older age at diagnosis, lower basal EDSS and less Magnetic resonance imaging (MRI) activity, increased the probability of response to the treatment.[24]

On the other hand, other studies do not share these findings. In a big observational study carried out in our country, the researchers did not find any epidemiological variable (sex, age at MS onset, duration of MS, and duration of GA treatment), nor clinical factors (number of relapses in the last year, basal EDSS and previous failure of IFN-b) significantly associated with the likelihood of attacks or disability progression.[25] Other observational study developed in Brazil did not meet any significant association either.[26]

It is clear that all these differences have to be related with methodological issues, but it is reasonable to expect a better response in those patients with milder MS.

Our work represents a large sample of 204 patients, with a good calibration of the regression logistic model, and therefore with a reliable internal validity of the results. Moreover, our study was conducted in only one center, yielding a greater homogeneity in the interpretation of the clinical data, and therefore with a greater internal validity. Finally, the epidemiological data of our sample are very similar to other previous series,[25-27] with comparable sex ratios, average age at onset of MS and average basal EDSS and annualized relapse rate. Beside this, it represents a meaningful variety of conditions that resemble very well the real life situations of the daily clinical practice.

In our study, we found an association between the number of relapses during the previous 2 years before the initiation of GA and the probability of response. These data would be in line with the results of the first clinical trials and their meta-analysis,[9-11,23] and some observational studies mentioned before,[24] in which older age, lower basal EDSS, lower relapse rate and less MRI activity were associated with the probability of response to GA.

We have to keep in mind that the overall diagnostic accuracy of the model was only moderate (64.7%; IC 95%: 55-74.5%) and the negative predictive value was low (37.2-50%). But the positive predictive value was good (73.9-82.7%). This means that with this model, we would lose some patients predicted to be non-responders and who could have had a good evolution with GA. But those patients predicted to be responders to GA would benefit from this treatment with a low risk of failure.

As previously described, if we settle a threshold of probability of response ≥70% to consider one patient as a good candidate to receive treatment with GA, this drug would be effective in RRMS patients ranging from basal EDSS=0 and a maximum of 2 relapses during the last 2 years, to EDSS=3.0 and only 1 relapse. These criteria would be achieved by 34.5% (IC 95%: 28.6-40.5%) of our sample. We chose this threshold of 70% because of its statistical performance according to the ROC curves, as there are not many other studies with this methodology.

For all these reasons, we think that this algorithm could be easy and useful to apply in the daily clinical practice, and with a low risk of error in a patient predicted to be responder.

CONCLUSION

The results of this study support the hypothesis that the less severe MS patients would have more opportunities to have a good response to GA. We were able to develop a predictive model of response to this treatment with the variables number of relapses during the last 2 years of disease and basal EDSS. We think that this model could be useful and applicable in the daily clinical practice. Nevertheless, it would be necessary to improve this predictive model with the incorporation of new variables like blood, genetic, serological and/or MRI biomarkers, to get more

statistical power and better results of the diagnostic parameters.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Review

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Neuromodulation in the Treatment of Migraine: Progress in Nerve Stimulation

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ABSTRACT

Migraine is a type of primary headache disorder that can become chronic and disabling. The exact pathomechanism of migraine is not known very well and its treatment is also difficult in some cases. There are several medications for the acute and preventive treatment of migraine including the "triptan" family drugs, nonsteroidal anti-inflammatory drugs, anti-epileptic drugs, beta-blockers, and Ca^{2+}-channel blockers[1] and those against calcitonin gene-related peptide or its receptor that are reviewed elsewhere.[2] However, there are some medically intractable headaches or patient management is unsatisfactory or medications are poorly tolerated[3] or there are contraindications. Therefore, neuromodulation and nerve stimulation methods that have proven effective in clinical research may provide an additional treatment option for acute and preventive treatment of migraine. In this brief review, we will discuss recent advances using neuromodulatory techniques that are currently used in the treatment of headaches in clinical studies. These include the electrical stimulation of occipital nerve, sphenopalatine ganglion, supraorbital nerve, and transcutaneous electrical stimulation of vagus nerve as well as single-pulse transcranial magnetic stimulation. Several clinical studies have conducted neurostimulation for the acute and preventive treatment of migraine in recent years but more studies are necessary to see their efficacy and long-term effect.

KEYWORDS: Neuromudulation; Migraine treatment; Nerve stimulation.

ABBREVIATIONS: AED: Anti-epileptic drugs; CGRP: Calcitonin gene-related peptide; CNS: Central Nervous System; CM: Chronic Migraine; fMRI: Functional Magnetic Resonance Imaging; GABA: Gamma amino butyric acid; HFEM: High Frequency Episodic Migraine; mAbs: Monoclonal antibodies; NSAIDS: Nonsteroidal anti-inflammatory drugs; nVNS: Non-invasive vagal nerve stimulation; ONS: Occipital Nerve Stimulation; PET: Positron Emission Tomography; SoC: Standard of Care; SPG: Sphenopalatine ganglion; TMS: Transcranial Magnetic Stimulation; TESoSN: Transcutaneous electrical stimulation of supraorbital nerve; VNS: Vagus/Vagal Nerve Stimulation.

INTRODUCTION

Migraine is a disabling brain disorder that is believed to be due to the dysfunction of the subcortical structures including diencephalic and brain stem areas that are involved in the processing and modulation of painful stimuli, leading to a dysmodulation of pain and vascular tone especially in the trigeminovascular system of susceptible patients.[4-8] There are two types of migraine: Migraine without aura and migraine with aura that occurs in about 30% of the migraine patients.[9] Activation of cortical neurons, the cortical spreading depression of Leão has long been proposed for the pathophysiology of migraine with aura[10,11] and a number of genetic abnormalities (channelopathies) have been detected in migraine patients with aura.[12-17] Migraine is a disabling disorder characterized by a unilateral pulsatile headache that is often accompanied by nausea and vomiting and lasts for 4-72 hours.[18] Migraine is a multifactorial disorder that is more common in females and is sometimes associated with comorbid disorders such as depression and epilepsy.[19] Genome-wide association studies have shown 13 migraine-associated variants that are involved in synaptic function, glutamatergic neurotransmission, nociception,

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vascular physiology, and metalloproteinases.[19]

Migraine can be episodic (frequency of attacks <15 days per month) or become chronic when frequency of the attacks is >15 days per month, 8 days of which have migraine features and the condition lasts more than 3 month.[20] Classification of different headache disorders has been continuously updated[18,20] to better facilitate the diagnosis and treatment of headache. The third edition (beta version) of the International Classification of Headache Disorders[20] is an updated source for classification of headache disorders. The exact pathomechanism of migraine is not known and its treatment remains challenging. Some of the main drugs that are currently being used in the acute and preventive treatment of migraine include the "triptans" and nonsteroidal anti-inflammatory drugs (NSAIDS), anti-epileptic drugs (AED), beta-blockers, and Ca^{2+}-channel blockers among others.[1] Several neurotransmitters and neuromodulators have been implicated in the pathomechanism of migraine. Among those, calcitonin gene-related peptide (CGRP) is one of the few neuropeptides that has been implicated in the pathogenesis of migraine and its increased level has been detected in the blood of migraine patients with and without aura.[21] Therefore, some more specific newer drugs such CGRP-receptor antagonists, known as "gepant" family of drugs such as Olcegepant[22,23] or Telcagepant,[24-26] MK-3207,[27,28] BI 44370 TA,[29] BMS-846372[30,31] and a few others in this category were developed in recent years but were discontinued in their clinical trials phase II and III or at an earlier stage mainly because of their liver toxicity and other problems. A recent double-blind, placebo-controlled, phase II b clinical trial randomized 834 participants to treat one migraine attack with various doses of Ubrogepant (MK-1602).[32] In that study, 527 participants received the drug and 113 received placebo. Their result shows that 100 mg ubrogepant was significantly superior to the placebo for causing 2-hour pain-free (25.5% *versus* 8.9%) but not for 2-hour headache response.[32] According to that study, this CGRP-receptor antagonist gepant family drug is effective in treating migraine and the adverse events among the ubrogepant and placebo treated patients are similar; therefore, their results seem promising.[32]

In recent years, newer (migraine-specific) drugs were developed. These include the 3 monoclonal antibodies (mAbs) against CGRP with long-term effects, the LY2951742,[33] the ALD-403,[34] and TEV-48125 (LBR-101)[35,36] and AMG 334, a mAb against CGRP receptor complex that has been developed by Amgen[37] have shown efficacy and tolerability in clinical trials with some minor side effects but are still under examination in clinical trials.

A few other drugs including one acting on 5-HT_{1F} receptor such as Lasmiditan (COL 144) in phase II and III studies[38-40] (that seem promising) and drugs targeting *nitric oxide synthase, glutamate, acid-sensing ion channels*, or gamma *amino butyric acid (GABA)-A* are still under investigation, please see references[2,8,41-43] for comprehensive review of the current treatment of migraine.

In spite of several medications available for the prevention and treatment of migraine, invasive and non-invasive approaches such as peripheral nerve blocks, botulinum toxin injection and electrical stimulation of various nerves have gained some focus in the treatment of chronic migraine in recent years. There a number of patients with medically intractable headache syndromes or chronic migraine that are non-responders to medications or poorly tolerate pharmacological medications or have contraindications and may need an alternative therapy.[44] Therefore, in recent years, neuromodulation and neurostimulation has been examined in a number of clinical studies to test their efficacy and tolerability as a novel method for the acute and preventive treatment of migraine.

This is a brief review of new advances and our current understanding of some invasive (greater occipital nerve or sphenopalatine ganglion stimulation) and non-invasive (transcutaneous vagal or supraorbital nerve stimulation or single-pulse transcranial magnetic stimulation) approaches implicated in the treatment of migraine.

The invasive devices are implanted subcutaneously or through other surgeries and the non-invasive devices are applied on the skin close the nerve and are self-administered by the patient as well. The results of some of these non-medication approaches are promising but more studies and data are needed to understand their efficacy and tolerability and long-term effects and side effects.

ELECTRICAL STIMULATION OF OCCIPITAL NERVE

Electrical stimulation of peripheral nerves for a long-term pain relief in human has been used through implantation of stimulator devices in the body in several clinical investigations for some decade now.[45-49]

Some of the mechanisms by which electrical stimulation reliefs pain seems to be driven from the well-known "gate theory of pain" and modulation of neurotransmitters release including neuropeptides and GABA-ergic system in the central nervous system.[50,51]

Electrical stimulation of superior sagittal sinus in cat increased activity in the caudal trigeminal nucleus, the cervical dorsal horn and in the dorsolateral spinal cord at the C2 level showing a convergence of neuroanatomical substrates of head pain on the second order neurons of trigeminocervical system.[52]

Electrical stimulation of the occipital nerve has shown effectiveness in treating the intractable pain of occipital neuralgias that were refractory to other medications.[53,54]

One of the first multicenter, randomized, blinded studies for preventive treatment of chronic migraine, the ONSTIM feasibility study, used occipital nerve stimulation (ONS) by means of implantation of a pulse generator device subcutane-

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ously superficial to the fascia and muscle layer at the C1 level.[55] The study assigned 75 out of 110 eligible patients to a treatment group. Their criteria for a responder was a patient who achieved a 50% or more reduction in the number of pain headache days per month or a three-point or more decrease in average overall pain intensity when compared to baseline. That study showed 39% 3-month responders in adjustable stimulation group while the group with preset stimulation or medical management (the control groups) had 6% and 0% 3-month responder rates[55] raising hope for ONS as a treatment option for some chronic migraine patients.

The other large-scale, multicenter, clinical study using ONS was conducted on 105 chronic migraine patients with active stimulation and 52 with sham-stimulation.[56] The neurostimulation device was implanted near the occipital nerves. The criteria for responders were those patients that achieved ≥50% reduction in mean daily visual analog scale scores by 12 weeks following the procedure.[56] The study did not meet their own primary endpoint pain criteria and there was not a significant difference in the percentage of responders in the active stimulated group compared with the sham stimulated group. However, there was a significant difference in the percentage of patients that achieved 30% pain reduction. There was also a significant decrease in headache days, and migraine associated disabilities between the active stimulated *versus* the sham stimulated group.[56] Some other ONS studies did not show a significant difference between the stimulated *versus* sham stimulated groups.[3]

Similarly, a recent study on 53 patients with chronic migraine (CM) and some with other associated chronic headache phenotypes in addition to CM had similar result; ONS was delivered through implanted device in a single center between 2007 and 2013. Following an average of 42-month follow-up, there was a 45.3% response rate in the whole cohort defined as >30% reduction in moderate to severe headache days per month, that is 34.3% in the CM group alone and 66.7% in those with multiple headache syndromes.[57] They also noticed significant reduction in the intensity and duration of pain as well as headache-associated disabilities. The overall mean subjective patient estimate of improvement was 31.7%.[57]

Therefore, although there are some success reports in ONS, at the moment the results are diverse and more studies are necessary to see the efficacy of ONS in the prevention of migraine.[41] More studies using advanced technology in nerve stimulation might have different outcomes as a new study shows better efficacy of burst ONS compared to tonic stimulation in treating animals with trigeminal allodynia.[58]

Consistent with these, customization of stimulation parameters is important in the result of such interventions as suprathreshold stimulation was found to yield better results in the treatment of migraine although subthreshold stimulation was also helpful.[59]

SPHENOPALATINE GANGLION STIMULATION

Sphenopalatine ganglion (SPG) is the largest extracranial parasympathetic ganglion involved in the innervation of meninges, lacrimal gland, nasal mucosa and conjunctiva that all have been implicated in migraine with autonomic cephalic symptoms including lacrimation, nasal congestion and conjunctival injection in common migraine patients.[60] The postsynaptic projections of the SPG supply lacrimal and nasal glands and are involved in several pain syndromes including trigeminal and sphenopalatine neuralgias, atypical facial pain and headache.[60] Therefore, blocking SPG has been used to treat atypical facial pain.[61,62] Involvement of SPG in neurovascular headache has been proposed since early 1900.[63]

Electrical stimulation of SPG has been also performed for determination of cerebral blood flow and glucose metabolism.[64]

Two mechanisms of action have been proposed for the role of electrical stimulation of SPG in relieving pain. These include possibly the interruption of post-ganglionic parasympathetic outflow, and modulation of sensory processing in the caudal trigeminal nucleus.[60]

A clinical investigation using electrical stimulation of SPG for ≤60 minutes in 11 medically refractory migraine patients (one patient was not stimulated) alleviated the pain in only half of the patients[65] although the failure was attributed to technical problems. The SPG was accessed by a 20-gauge needle through infrazygomatic transcoronoid approach into the sphenopalatine fossa visualized under fluoroscopy; a unilateral electrical stimulation of the SPG was delivered by a Medtronic 3057 test stimulation lead following induction of migraine.[65] Stimulating parameters in that study were the following: Mean amplitude: 1.2 V, mean pulse rate: 67 Hz, and mean pulse width: 462 micros.[65]

Clinical trials (NCT01540799, and NCT02510742, https://clinicaltrials.gov) with electrical stimulation of SPG in migraine patients might shed light into our understanding on the role of such procedures in treatment of migraine.

Current data is insufficient[3] and more clinical studies are needed to understand the efficacy, tolerability, convenience, and long-term effect of SPG stimulation in the acute treatment of migraine. Moreover, molecular and imaging studies following SPG stimulation may shed light into the mechanism of its modulation of pain.

TTRANSCUTANEOUS ELECTRICAL STIMULATION OF SUPRAORBITAL NERVE (TESoSN)

Transcutaneous electrical stimulation of peripheral nerves in human has long been performed for various pain syndromes that could not be treated otherwise and the outcomes were satisfac-

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tory.[66,67]

These non-invasive impulse generator devices are placed on the skin close to the nerves and they transmit the electrical impulses transcutaneously through electrodes to the nerves.

A recent study using transcutaneous electrical stimulation of supraorbital nerve (TESoSN) for 8 weeks in 12 patients suffering from depression and post-traumatic stress disorder (PTSD) in an out-patient open trial resulted in significant improvement of the symptoms.[68] Available evidence shows some effectiveness of TESoSN in treatment of migraine.[69]

Using a new stimulator called "Cefaly" (STX-Med, Herstal, Belgium), the supraorbital nerve branch of the trigeminal nerve was stimulated in a double-blinded, randomized, sham-controlled trial in 67 patients for the prevention of migraine in 5 Belgian tertiary headache clinics. The Cefaly headband is placed on the skin close to the supraorbital and supratrochlear branches of the ophthalmic nerve in the forehead and transmits the electrical impulses transcutaneously through a self-adhesive electrode to the nerves.[70,71] Cefaly device has FDA approval.[71] The stimulator was used daily for 20 min for 3 months. Results showed that the mean migraine days decreased significantly from 6.94 to 4.88 in the verum stimulated group while there was almost no difference in the sham stimulated group.[70] Primary outcome measures in that study was a change in monthly migraine days and 50% responder rate. Accordingly, the 50% responder rate was significantly higher (38.1%) in verum stimulated *versus* sham stimulated group (12.1%). Moreover, TESoSN reduced the attack frequency and total headache day but not the severity of the headache.[70] PET studies show that Cefaly increases the activity of limbic system including orbitofrontal and anterior cingulate cortices.[71]

Moreover, a recent study in 24 patients with low frequency migraine attack, a brief period of high frequency TESoSN improved multiple migraine severity parameters.[72]

The safety and tolerability of TESoSN using Cefaly® device was studied in a large group (2313 headache sufferers) in general population who rented the device through internet for a 40-day trial period) and was found to be safe and well-tolerated by many people (although it did not help some people and they returned the device).[73]

External trigeminal nerve stimulation in episodic migraine was also effective for at least 3 weeks but more studies with control group were suggested for better conclusion.[74]

It appears TESoSN as a non-invasive approach has some moderate effects in the acute and preventive treatment of migraine but more clinical studies will shed lights in the efficacy of the method. One set back with the current technology might be its continuous its daily use for several minutes continued for several months to alleviate some of the migraine symptoms.

ELECTRICAL STIMULATION OF VAGUS NERVE

Electrical stimulation of vagus nerve has been used to treat intractable epileptic seizures not responding to medication or surgery but there is no clear mechanism for the regulatory effect of vagus nerve stimulation (VNS) in relieving the symptoms.[75,76]

Blood oxygenation level changes by VNS since it activates (or increase blood flow to) several cortical and subcortical structures.[77] Such changes are seen in different thalamic nuclei insular gyrus, postcentral gyrus, parts of temporal and occipital gyri and basal ganglia using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) studies in human.[78-80] Brain blood flow increased in rostral and dorsal-central medulla, right postcentral gyrus, bilateral thalami and hypothalami, insular cortices and lower cerebellum upon left cervical VNS in partial epileptic patients while blood flow decreased bilaterally in hippocampus, amygdala and posterior cingulate gyri.[79]

VNS in a few epileptic patients who were also suffering from migraine resulted in improvement of headache.[81] VNS significantly improved the symptoms in 5 patients with chronic refractory migraine or cluster headache[82] or in 4 adult female patients with drug-refractory chronic migraine[83] or in 13 patients with refractory epilepsy and migraine.[84]

Nevertheless, a small study shows that low intensity VNS in epileptic patients decreased the thermal pain threshold in human subjects.[85]

Some vagal afferent nerve fibers terminate in the trigeminal nucleus and animal studies show that electrical stimulation of vagus nerve modulates trigeminovascular nociception (see the discussion please). Both invasive and non-invasive VNS has recently been shown to inhibit cortical spreading depression in rat.[86]

The VNS was delivered on 27 migraine patients with and without aura in an open-label, single arm, multiple attack pilot study and their results indicate the efficacy and tolerability of VNS in episodic migraine patients.[87]

Up to 4 migraine attacks were treated in that study by VNS with two 90-sec dose at 15-min intervals that were delivered to the right vagus nerve (cervical branch) within a 6-week time period. Patients were allowed to self-treat at moderate or severe pain or following 20-min of a mild pain. The pain was aborted at 2 hours in 22% of patients with moderate or severe attacks at baseline.[87]

Another more recent open-label, single-arm, multicenter study used VNS on 36 patients with chronic migraine and 14 suffering from high frequency episodic migraine (HFEM).

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Patients self-treated up to 3 consecutive mild or moderate migraine attacks occurring in 2-week period by delivery of two 120-second doses on VNS at 3-min intervals to the right vagal nerve (cervical branch). They found that 56.3% of the patients had pain reduction (≥50% reduction in visual analog scale "VAS" score) at 1 hour and 64.6% at 2 hour. Of these patients, 35.4% and 39.6% reached a pain-free (VAS:0) situation at 1 and 2 hours respectively. The pain-relief rate was 38.2% and 51.1% at 1 and 2 hour respectively when all attacks (N=131) were considered and pain-free rates in latter cases were approximately half of the corresponding percentages, indicating that the non-invasive VNS is an effective method for acute treatment of chronic migraine or HFCM. [88]

Another trial, a monocentric, randomized, controlled, double-blind study in 40 patients with chronic migraine also shows that electrical stimulation of the auricular branch of the vagus nerve by means of a battery driven handhold stimulator to the sensory areas of left ear at 1 Hz for 4 hours per day for 3 months has significantly reduced the pain days (≥50% reduction in headache days) and improved the headache impact test and disability assessment test.[89]

Non-invasive vagal nerve stimulation (nVNS) in 20 patients with treatment-refractory migraine has also been shown to be effective in the prevention and treatment of episodic and chronic migraine patients with associated sleep disturbances.[90] In that 3-month open-label, prospective observational study, 20 patients with treatment-refractory migraine were treated twice daily with nVNS prophylactically at pre-specified times and acutely as the adjunctive therapy for migraine attacks. Results show significant reduction in frequency, intensity, and duration of pain and improvements in migraine associated disability, depression and quality of sleep in treatment-refractory migraine patients. [90]

The most recent pilot prospective, multicenter, double-blind, sham-controlled study, the EVENT study,[91] shows also that nVNS is well tolerated and safe but did not significantly change the headache days in chronic migraine patients who had >15 headache days per month. Fifty nine patients took part in this study, 30 patients with nVNS and 29 had sham-treatment. Patients had a 1 month baseline phase and were randomized subsequently to nVNS or sham-treatment for 2 months before receiving open-label nVNS. Mean reduction in the number of headache days was 1.4 in the nVNS versus 0.2 day in the sham-treatment group and the difference was not significant but there was a trend p=0.56 The study concluded that consistent use of nVNS as a prophylactic treatment of chronic migraine can reduce the headache days but larger sham-controlled studies are needed.[91]

The nVNS has also been effective in prophylactic treatment of cluster headache in PREVA group study. This prospective, open-label, randomized study worked on 48 patients who received adjunctive nVNS plus standard of care (SoC) and 49 control patients only with the SoC alone. The duration and plan of the study comprised of 2-weeks baseline phase followed by 4-weeks randomized phase (nVNS plus SoC *versus* control group who received only SoC alone) followed by 4-weeks extension phase (nVNS plus SoC). Their results show that the ≥50% response rate was higher (40%) in the nVNS plus SoC group compared to 8.3% in the SoC alone treated control group.[92]

There are evidences that electrical stimulation of the nerves leads to the release of neurotransmitters or neuromodulators and vasoactive substances from their peripheral and central nerve endings affecting the vascular permeability or tissue inflammatory molecules peripherally and neurotransmission in the CNS.[93-95] Electrical stimulation of the vagus nerve seems to decrease the severity of rheumatoid arthritis perhaps by inhibition of cytokine production.[96]

Overall, nVNS seems promising in the acute and preventive treatment of migraine and is suggested to be continued in clinical trials[3] to gather more information about its effectiveness in the treatment of migraine headaches and to understand the mechanism(s) of its effectiveness in trigeminocervical pain. In addition, as discussed above, blood oxygenation level and metabolic activities of a number of brain regions increase or decrease following VNS.[77-79] Therefore, more basic research in VNS may add more knowledge to our current understanding of the brain central pain modulatory centers.

TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) is a method that has been used to activate the motor cortex and study the facial motor responses[97] or elsewhere in the body[98] but it also seems to alleviate the pain of migraine patient with aura.[99]

Transcranial stimulation is based on electromagnetic technology. A pulse of current passes through a coil that is located in a portable device which can be placed on the individual's head (i.e. in the occipital region) for a short time and when turned on, it depolarizes neurons in the target area.[100]

A randomized, double-blind, parallel-group, two phase, sham-controlled study in 18 centers in the United States investigated the pain relief in 267 adults suffering from migraine with aura, of which 66 patients were dropped in phase one. The remaining 201 patients were randomly chosen to have the single-pulse transcranial magnetic stimulation (sTMS, n=102) or sham-stimulation (n=99).[101] The patients were informed to treat up to 3 attacks over 3 months when experience aura. Out of 201 patients, 37 who didn't treat a migraine attack were excluded and the rest were divided equally into the sTMS or sham stimulated groups (n=82 for each group). The pain-free response after 2 hours was 39% in the sTMS group compared to 22% in the sham stimulated group. Pain free status at 24 hours and 48 hours post-treatment was still significantly higher in the TMS group but other symptoms such as nausea, photophobia and phonopho-

bia were not changed, nor there were serious side effects in the sTMS or sham stimulated group. That study shows the effectiveness of single-pulse TMS in acute treatment of migraine with aura patients.[101]

A survey of 190 patients with episodic (n=59) and chronic (n=131) migraine with and without aura after 3 month following single-pulse TMS shows 62% of the patients reported pain relief and over 52%-55% had reduction of associated symptoms such as nausea, photophobia and phonophobia. After 3 month, the mean headache days in episodic migraine reduced from 12 to 9 days and for the chronic migraine patients from 24 to 16 days.[100]

A recent study in rats and cats shows that single-pulse TMS is able to inhibit both mechanical and chemically-induced cortical spreading depression and reduced the firing of third-order neurons (thalamocortical) but not 2nd-order neurons of the trigeminocervical complex.[102]

All together, these studies show the efficacy of single-pulse TMS in the non-pharmacological treatment of migraine but more studies on the aura symptoms and perhaps effect of TMS on cerebral blood flow might be helpful, however, the procedure seems to be safe and tolerable.[103]

DISCUSSION

Migraine is one of the most prevalent neurological disorders that is characterized by headache, gastrointestinal problems and sensory dysfunction. Because of it multifactorial etiology, migraine is very difficult to treat. Migraine therapy is based on the acute and preventive treatments. There are several pharmacological and non-pharmacological treatments of migraine currently available in clinical practice. Many of the pharmacologic treatment of migraine have side effects and contraindications and with the insufficient efficacy and dissatisfaction they are often discontinued.[71,104] Using medication such as triptans and NSAIDS may lead to chronic migraine.[105] A large-scale study based on US health insurance claims database during 2003-2005 on 4634 patients who started migraine prophylaxis with antidepressants, antiepileptic drugs, or beta-blockers shows that they were no longer taking these medications at 6 months.[106] Therefore, alternative and additional treatment options are necessary for the unmet treatment of migraine. This review was aimed to update us on the new advances in the treatment of migraine through neuromodulation. A number of clinical studies in recent years initiated the acute and preventive treatment of migraine specially the chronic medically intractable headaches using novel invasive and non-invasive neurostimulation of the peripheral and central nervous system.

The invasive devices are implanted subcutaneously or through other surgeries and are powered by implantable batteries or controlled wirelessly, while the non-invasive devices are applied on the skin close to the nerve and can be self-administered by the patient as well.[107]

The exact mechanism of pain relief by electrical stimulation of nerves is not known very well but it might be due to modulating the release of neurotransmitters including neuropeptides in the CNS and closing the gate of pain and also the brain areas involved in pain processing.[50,51]

Other studies suggest a central control for pain following such stimulations as seen in VNS[78-80] studies and ONS in cluster headache (CH) patients. Using metabolic neuroimaging by PET, several areas of brain of CH patients showed hypermetabolism.[108] Increased hypermetabolism seen by uptake of [18F] fluorodeoxyglucose (FDG) was detected on PET in the ipsilateral hypothalamus, midbrain, and ipsilateral lower pons of CH patients.[108] All hypermetabolic areas were normalized following ONS except the hypothalamus which was proposed to be possibly responsible for the autonomic attacks persistence despite pain relief.[108] In the responders of ONS in that study, the perigenual anterior cingulate cortex was hyperactive compared to non-responders, indicating the importance of this endogenous opioid system in the brain in modulating pain.[108]

Moreover, ONS and transcuta-neous electrical stimulation might relieve pain through neuro-modulatory effects in the limbic system and cortical pain control areas, see reference for review.[71]

Electrical stimulation of the greater occipital nerve was one of the invasive methods discussed in this review. Two major studies were mentioned: The ONSTIM feasibility study.[55] Occipital nerve stimulation (ONS) was delivered by means of a pulse generator device that was surgically implanted subcutaneously superficial to the fascia and muscle layer of the back of the neck at the C1 level.[55] Hundred and ten patients with chronic migraine participated in the ONSTIM feasibility study. Seventy five of them were the treated (adjustable stimulated) group. The number of 3-month responders with 50% or more reduction in the number of headache days per month was at 39% in the adjustable stimulated group compared to 6% in the preset (control) stimulated group.

The other large-scale study discussed in this review used ONS on 105 chronic migraine patients and 52 with sham-stimulation. That study showed only a significant difference in the percentage of patients who had 30% decrease in the mean daily visual analog scale scores by 12 weeks (pain reduction) following the stimulation.[56] The primary end point in that study was the difference in the percentage of responders that achieved ≥50% reduction in mean daily visual analog scale scores by 12 weeks following the procedure.[56]

These studies show the efficacy of ONS in treating some chronic migraine patients although the majority of the patients may not have fully benefited from the ONS. Some of the side effects such as paresthesia or infection, other surgery-relat-

ed complications, electrode migration, and battery depletion and replacement, and implant site pain can be seen in the invasive nerve stimulated patients.[55,56,71] Nevertheless, more ONS studies on selected patients with more uniform results may be necessary for its recommendation[3] which may also help finding more optimal procedural protocols and guidelines.

A number of reasons might contribute to the difference in the responses among patients. These may include the diversity in the etiology of migraine and the different trigger points compared to the level(s) of modulation. Usually these stimulations lead to neuronal modulation at the first central synapses in the spinal cord or trigeminal nucleus and may be confined to a small area in that level and higher CNS areas. If the trigger point for the migraine lies outside the peripheral and/or central territory of the occipital or other stimulated nerves, the modulatory effect of stimulation may not reach the trigger area of the central nervous system. Other reasons might be the peripheral and central sensitizations that may not be affected by such stimulations due to the involvement of multiple signaling molecules.[109] Although, procedural and technical errors or surgical complications in general can also contribute to different outcomes but these are usually recognized by the investigators conducting the study.

The other invasive method mentioned in this review was the electrical stimulation of the sphenopalatine ganglion (SPG) for the treatment of acute migraine.

The mechanisms of pain relief following SPG stimulation might possibly be due to interruption of postganglionic parasympathetic outflow and modulation of sensory processing in the caudal trigeminal nucleus.[60]

In one study mentioned here electrical stimulation of SPG for ≤60 minutes in 10 patients with refractory migraine alleviated the pain in 50% of the patients.[65] Currently, there is insufficient data on the efficacy, long-term effect and side effects of SPG stimulation in the treatment of acute migraine. However, sphenopalatine ganglion and its innervation and function is extremely important and relevant for migraine and cluster headache studies and more research including the clinical trials mentioned above in this review will add more to our understanding of the pathomechanism of migraine.

Other neuromodulation/stimulation methods applied for the acute and preventive treatment of migraine with some shown efficacy that were discussed here include the non-invasive electrical stimulation procedures such as vagal nerve stimulation,[87-92] the transcutaneous electrical stimulation of supraorbital nerve (TESoSN) and single-pulse transcranial magnetic stimulation.

Some afferent vagal nerve fibers project to the brain stem trigeminal nucleus.[110] The mechanism of pain relief following electrical stimulation of the vagus nerve might be due to vagal afferent being able to modulate trigeminovascular pain in the brain stem. Continuous electrical stimulation of vagus nerve in rats modulates trigeminovascular nociception possibly due to decrease in neurotransmitters such as glutamate.[111] Electrical stimulation of cardiopulmonary vagal afferent in anesthetized rats modulates nociception in the trigeminal and trigeminothalamic neurons in response to painful orofacial stimulation.[112,113] Therefore, electrical stimulation of the vagus nerve has some promising results and more clinical trials should add more to our current understanding of neurostimulation method in the treatment of migraine.

The TESoSN has some moderate effects in the acute and preventive treatment of migraine. One set back with the current technology might be the necessity for its continuous daily use for several minutes continued for several weeks or months to treat migraine.

Table 1 is a brief review of major studies (and their results) that used nerve stimulation to treat migraine in the last couple of years.

CONCLUSION

Although a number of medications are available for the acute and preventive treatment of migraine, neurostimulation techniques have also been used in the treatment of medically intractable headaches in clinical studies in recent years.

Their ability to influence brain network interactions is advancing their applicability.

Among these, electrical stimulation of greater occipital nerve or sphenopalatine ganglion are the invasive ones and the non-invasive procedures include the vagal nerve stimulation, the supraorbital nerve stimulation or the single-pulse transcranial magnetic stimulation.

These recent advances in the management of migraine show some degrees of success. Vagal nerve stimulation is promising and because it is also used in the treatment of other conditions such as epilepsy, advances in this field can help treatment of headaches and other disorders as well as understanding of the mechanism of pain relief. Occipital nerve stimulation results are diverse, and sphenopalatine ganglion stimulation studies are insufficient[3] but are relevant and interesting in headache research. Therefore, more such neuromodulation/nerve stimulation studies with long-term follow up may be necessary to learn more about their tolerability, convenience, effectiveness and side effects in the acute and preventive treatment of migraine. In addition, these clinical studies will shed light into our understanding of pathomechanism of migraine.

Future direction and research in this field can greatly benefit from the guidelines and Consensus Statement of the

Neuromodulation procedure	Major studies done	Results
Occipital nerve stimulation (ONS)	- ONSTIM feasibility study: used ONS by means of subcutaneous implantation of a pulse generator device for preventive treatment of chronic migraine.[55] - 75 out of 110 eligible patients were assigned to treatment group.[55] - Another large-scale study used ONS to chronic migraine patients (105 patients with active stimulation and 52 with sham stimulation).[56] the criteria for responders were those patients that achieved ≥50% reduction in mean daily visual analog scale scores by 12 weeks following the procedure.[56] -Another study used ONS on 53 patients with chronic migraine (CM) and some within this group suffering from other associated chronic headache phenotypes in addition to CM.[57]	- The treated group (adjustable stimulation group) showed 39% 3-month responders but the control group (preset stimulation or medical management) had 6% and 0% 3-month responder rates.[55] - There was a significant difference in the percentage of patients that achieved 30% but not 50% pain reduction. There was also reduction of headache days and other associated symptoms in active stimulated group.[56] -After an average of 42 month follow up, there was a 45.3% response rate in the whole cohort defined as >30% reduction in moderate to severe headache days per month. The overall mean subjective patient estimate of improvement was 31.7%.[57]
Pterygopalatine (Sphenopalatine) ganglion stimulation	- One clinical study used electrical stimulation of SPG for ≤60 minutes in 10 patients suffering from refractory migraine.[65] - A few other studies are in clinical trials at the moment.	- The pain was alleviated in only half of the patients although the failure might have been due to technical problems.[65]
Transcutaneous electrical stimulation of supraorbital nerve (TESoSN)	- One investigation in five Belgian tertiary headache clinics used TESoSN in 67 patients for the prevention of migraine. They used a new stimulator called “Cefaly” for 20 min/day for 3 months.[70]	- Mean migraine days decreased significantly from 6.94 to 4.88 in the verum stimulated group but almost no difference in the sham stimulated group. The 50% responder rate was significantly higher (38.1%) in verum stimulated versus sham stimulated group (12.1%).[70]
Non-invasive vagal nerve stimulation (nVNS)	- VNS was applied on 36 patients with chronic migraine and 14 suffering from high frequency episodic migraine (HFEM).[88] - 40 patients with chronic migraine had electrical stimulation of the auricular branch of the vagus nerve by means of a battery driven handhold stimulator to the sensory areas of left ear at 1 Hz for 4 hours per day for 3 months.[89] - EVENT study: 59 patients with chronic migraine took part in this study. 30 patients with nVNS and 29 had sham treatment. Patients had a one month baseline phase and were randomized subsequently to nVNS or sham treatment for 2 months before receiving open-label nVNS.[91] - PREVA study: 48 patients in received adjunctive nVNS plus standard of care (SoC) and 49 control patients only with the SoC alone for prophylactic treatment of cluster headache.[92]	- 56.3% of the patients had pain reduction (≥50% reduction in visual analog scale “VAS” score) at 1 hour and 64.6% at 2 hour.[88] - Of these patients, 35.4% and 39.6% reached a pain-free (VAS: 0) state at 1 and 2 hours respectively.[88] -Pain days was significantly reduced (≥50% reduction in headache days)[89] - It improved the headache impact test and disability assessment test.[89] - Mean reduction in the number of headache days was 1.4 in the nVNS *versus* 0.2 day in the sham-treatment group and the difference was not significant.[91] - The ≥50% response rate was higher (40%) in the nVNS plus SoC group compared to 8.3% in the SoC alone treated control group.[92]
Transcranial magnetic stimulation (TMS)	- One study with 2 groups of migraine patients with aura used stimulation (sTMS) n=82 on one group and sham stimulation on control group, n=82.[101] - Another investigation studies 190 patients with episodic (n=59) and chronic (n=131) migraine with and without aura using single-pulse TMS.[100]	- The pain-free response after 2 hours was 39% in the sTMS group compared to 22% control group.[101] - Pain free status at 24 hours and 48 hours post-treatment was still significantly higher in the sTMS group.[101] - After 3 month following TMS 62% had pain relief.[100] - 52%-55% had reduction of associated symptoms such as nausea, photophobia and phonophobia.[100] - Mean headache days in episodic migraine reduced from 12 to 9 days and for the chronic migraine patients from 24 to 16 days.[100]

Table 1: A brief review of the major clinical studies done for the treatment of migraine using electrical stimulation of various peripheral nerves/neurons or cranial neurons.

2013 European Headache Federation for clinical use of neuromodulation in headache.[114]

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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