

Research Advances in Brain Disorders and Therapy

Shehata HS, et al. Res Adv Brain Disord Ther: RABDT-105.

DOI: 10.29011/RABDT-105.100005

Review Article

Neuromodulation of Chronic Migraine. The Available Evidence and Therapeutic Prospects of Transcranial Magnetic Stimulation

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Citation: Shehata HS, Elmazny A, Shalaby NM (2018) Neuromodulation of Chronic Migraine. The Available Evidence and Therapeutic Prospects of Transcranial Magnetic Stimulation. Res Adv Brain Disord Ther: RABDT-105. DOI: 10.29011/RABDT-105.100005

Received Date: 24 April, 2018; **Accepted Date:** 18 May, 2018; **Published Date:** 24 May, 2018

Abstract

Chronic Migraine (CM) is a complex brain disorder, whose impact is relevant on patients and public health in terms of personal suffering and reduced productivity with consequently negative impact on health-related quality of life. Despite the burden of disease and increasing availability of effective treatment, migraine management is still unsatisfactory. A variety of neuromodulatory approaches illustrate that much can be done to improve patient care and they can be viable treatment modalities in medically refractory chronic migraine. The Repetitive Transcranial Magnetic Stimulation (rTMS) - a safe and effective Neuromodulation technique - has emerged as a promising treatment for the management of chronic migraine especially when all the other treatments fail.

The aim of this review was to summarize the scientific rationale of the current state of Neuromodulation application with special emphasis on rTMS in management of chronic migraine.

Although most of the available data support the efficacy and tolerability of rTMS for patients with chronic migraine as it has shown promising results in reducing the severity and frequency of headache in chronic migraine patients, this technique cannot yet be used as a therapeutic alternative due to lack of studies with large sample sizes that portray its positive effects. More controlled studies should corroborate the current view.

Keywords: Botulinum Toxin-A; Chronic Migraine; Neuromodulation; rTMS

Introduction

Chronic Migraine (CM) is a disabling disease defined as more than 15 headache day by month for more than 3 months, with at least eight headache days per month fulfilling the criteria for migraine headaches [1]. Chronic migraine is a common disorder; the reported prevalence is 1-2% in general population with about 3% of episodic migraine patients progress to chronic migraine [2]. In a community-based, cross-sectional multi-stage stratified systematic random sampling survey in Egypt; [3] it was found that the one-year prevalence of CM was 2.9%. The path to

chronic migraine is not a one-way-road - spontaneous or medically induced remission is possible and even common: about 26% of patients with chronic migraine remit within 2 years of the onset of chronic migraine [4].

Chronic Migraine. Disease Burden and Conventional Management

People with CM are more likely to experience certain somatic and psychiatric comorbidities - such as depression, anxiety, and various respiratory and cardiovascular conditions - than are people with episodic migraine; which increases the disability rates and burden of disease with a more-severe impact on socioeconomic functioning and quality of life [2].

The abortive treatment of chronic migraine is frequently problematic; the use of pain killers or specific headache medication taken after the attack has begun is usually ineffective and should be avoided because it requires regular intake of acute medication, which predisposes to Medication Overuse Headache (MOH). Instead, the aim of the treatment needs to be prevention of migraine attacks; however, most abortive and preventative treatments employed are classically non-specific, and their efficacy and safety and tolerability are often unsatisfactory [5]. The standard preventive treatments include beta-blockers, topiramate, valproate and recently a mechanism-based therapy that blocks the Calcitonin Gene-Related Peptide (CGRP) signaling pathway is highly anticipated and promising new drug class [5,6]. All of these substances have been shown to be superior to placebo in the prophylaxis of migraine in general, but only a few have been specifically investigated for their effectiveness in chronic migraine [6].

Onabotulinumtoxin A (BoNT-A) is the only approved treatment specifically for chronic but not episodic migraine according to two large-scale phase III Randomized Controlled Trials (RCTs), Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1 and 2. At a minimum dose of 155 U, BoNT-A could effectively reduce total headache days in chronic migraine patients with or without acute medication overuse [7,8] when injected every 12 weeks in a standardized, so-called PREEMPT-scheme. However; a systematic review and meta-analysis revealed small to modest benefits of treatment with BoNT-A in chronic daily headache and chronic migraine [9]. Moreover; long-term data on safety, efficacy and tolerability of BoNT-A do not yet exist, but ongoing studies, such as the Chronic Migraine Onabotulinumtoxina Prolonged Efficacy Open Label (COMPEL) study, aim to investigate the long-term safety, efficacy and tolerability of nine cycles of repetitive BoNT-A injections administered every 12 weeks [10].

Neuromodulation in Chronic Migraine

Although the first-line treatment in chronic headache is pharmacological; yet, given that good adherence is crucial in achieving the full beneficial effects of long-term treatments in chronic diseases, these drugs will have a limited efficacy in relieving headache as they can be associated with poor long-term adherence and can produce adverse effects [11]. On the other way round; the safety and tolerability features of various neuromodulatory methods have prompted the research on its therapeutic effects in area of great need like chronic migraine. Neuromodulation influences pain signals for the purpose of reversible modification of the nociceptive system function by the exogenous application of electrical currents [11,12].

Neuromodulations used for the therapy of chronic migraine can be divided into peripheral or central. Peripheral Neuromodulation methods include pharmacological blockade

of the Greater Occipital Nerve (GON) and electrical stimulation of occipital nerves, supraorbital nerves or the vagal nerves. Central Neuromodulation methods include Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) [11].

Particularly, TMS is a noninvasive method of Neuromodulation that may offer an excellent alternate therapeutic option for chronic central pain conditions including chronic migraine [13]. However, data from recent studies of rTMS are still preliminary with some negative results for chronic migraine. Such studies indicate also a powerful placebo response to the sham stimulation (probably due to the suggestion to become magnetized). In the future, Neuromodulation with rTMS will probably have a better place in chronic migraine treatment, especially because of its attractive safety profile.

Transcranial Magnetic Stimulation. Rationales and Mechanisms in Chronic Migraine

Transcranial magnetic stimulation generates electrical currents in the subjacent cortex by a rapidly changing magnetic field; which cause alteration of membrane potentials of specific neurons, ultimately resulting in either a depolarization potential or hyperpolarization of exposed cell membrane. These electrical changes in the brain are believed to give rise to the measurable neurochemical sequella as measured by modifications in brain neurotransmitters [14]. The rationale for applying rTMS to treat neurological and psychiatric disorders is that it can change the brain to produce effects that last beyond the duration of stimulation, the so called ‘cerebral plasticity’; which underlies various brain functions such as learning, adaptation, and recovery from injury [15]. It activates short intracortical interneurons and long axons connected with distant structures [16]. Different TMS application patterns have different effects; it can induce either long-term potentiation or long-term depression as high-frequency rTMS (5 Hz or faster) [HF-rTMS] increases excitability, whereas slow rTMS at approximately 1 Hz decreases it [17].

Generally, the short-lasting effects involve altering synaptic strength, whether increasing synaptic strength (long-term potentiation) or reducing strength (long-term depression), whereas longer exposures trigger longer-lasting anatomical changes such as sprouting and alterations of dendritic spines [15]. Motor cortex rTMS oriented postero anteriorly and parallel to the midsagittal plane preferentially activates horizontal cortical axons running parallel to the surface [18].

Among the various locations of cortical stimulation, the motor and the prefrontal cortices, especially the Left Dorsal Lateral Prefrontal Cortex (LDLPFC), appear to have the most profound analgesic benefit. The LDLPFC is also known to have a mood enhancing effect. High-frequency stimulation of both

MC and DLPFC can result in an analgesic benefit; however, their relative mechanisms are different; [19] while stimulation at the MC activates a strong focal activation in thalamus, insula, cingulate-orbitofrontal junction, and Periaqueductal Gray (PAG) Area, suggesting a top-down activation of the descending pain control system mediated via a motor-thalamus functional linkage; [20] on the other hand, rTMS at the DLPFC exerts a top-down inhibitory effect along the ascending midbrain-thalamic-cingulate pathway through the descending fibers from the prefrontal cortex [21].

Early studies of Dural Motor Cortical Stimulation (MCS) implicated antidromic activation of thalamocortical pathways, and recent studies show that integrity of the thalamocortical tracts is required to treat pain [22]. Imaging shows that MCS additionally affects structures involved in affective, cognitive, and emotional aspects of pain, such as the cingulate and orbitofrontal cortices, by influencing opioidergic or gamma-aminobutyric acid transmission [23]. For treatment, research has established that a figure-of-8 coil delivering biphasic pulses should be placed over the precentral gyrus (primary motor cortex) contralateral to the painful side with a posteroanterior orientation [15].

In migraine; there are several psychophysical, electrophysiological and neuroimaging reports that emphasized the hyper responsivity of the primary occipital cortex [24]. This hyper responsivity was recently found to extend to extra striate area (V5). This abnormal cortical excitability has been thought to reflect dysfunction of inhibitory circuits [25]. The Cortical Spreading Depression (CSD), an intense K⁺ dependent depolarization of neuronal and glial membranes, has been established as the biological substrate of the migraine aura that results in neurogenic inflammation and activation of nociceptive trigeminal afferents and it is the physiological expression of the underlying brain hyper responsivity, particularly involving the occipital cortex [26,27].

Hyper responsivity has been inferred from an over-response to sensory stimuli due to modulation of sensory information processing; so, migraineurs show more signs of aversion to visual stimuli that evoke paroxysmal EEG activity in patients with photosensitive epilepsy than control groups [28]. On the other view; it was also concluded that the heightened neural response seen in migraine is not like that the hyper responsivity seen in epilepsy, but is instead a reflection of a hyper-responsiveness to sensory stimuli; [29] as epileptic discharges require synchronized neural activity over a large area of the cortex whereas in migraine hyper-responsiveness may be a result of a more localized excitation [30].

Neurophysiological studies in migraine revealed a consistent higher amplitude of Visual Evoked Potentials (VEPs) and absence

of the usual habituation to repetitive stimuli [31]. Transcranial Magnetic Stimulation (TMS) has been used in migraine patients to test occipital cortex excitability by measuring what is called Phosphene Threshold (PT), defined as the minimum intensity of a TMS pulse needed to evoke Phosphenes, which is inversely related to the overall level of visual cortex excitability [32]. Important discrepancies among different studies do exist, with some reports found increased, and others found decreased in the inter-ictal PT. These conflicting results make it very difficult to reach a definite conclusion by simple summation of previous results [33]. Animal models studies demonstrated that TMS can inhibit CSD and thus has the potential to terminate aura and reduce the duration or severity of the ensuing migraine headache in patients who suffer from migraine with aura [34]. Single-pulse TMS (sTMS) is an effective and well-tolerated treatment for migraine with or without aura and it may offer a nonpharmacologic, non-behavioral therapeutic approach to the currently prescribed drugs for patients who suffer from migraine [35,36]. In a large randomized, sham-controlled trial involving 164 patients assigned to either sTMS or sham stimulation in a 1:1 revealed significantly higher pain-free response rates after 2h with sTMS (32/82 (39%)) than with sham stimulation (18/82 (22%)) (p = 0.0179) [36].

Given that sTMS is effective at treating acute migraine, one can hypothesize that repetitive TMS (rTMS) is beneficial in migraine prevention. Indeed, there are encouraging data to support rTMS for migraine prevention. Studies have demonstrated that rTMS sessions over the M1 region help to restore defective Intracortical Inhibition (ICI) and to normalize excitability in the brains of migraineurs [37]. The efficacy of HF-rTMS applied to the Dorsolateral Prefrontal Cortex (DLPFC) was initially demonstrated in a small sham-controlled pilot study [38]. The postulated mechanism of the excitatory effects of high frequency sessions in pain modulation was through the connectivity of DLPFC with pain processing centers in the brainstem and thalamus. The mechanisms of headache relief with rTMS appear to be multifactorial. rTMS has been shown to cause various neurochemical changes including increased dopamine levels in the hippocampus, reduction in Raclopride C11 binding in the caudate nucleus, fluctuations in glutamate/glutamine levels at the site of rTMS stimulation and increased plasma β -endorphin levels [39-42].

Many authorities emphasized the role of rTMS in chronic migraine prophylaxis; yet, lack of a standardized definition for the hot spot upon which the coil should be applied and absence of a consensus protocol to be adopted in every study lead to heterogeneous and non-conclusive results (Table 1).

Study	Design	Frequency (Hz)	Motor threshold	Coil placement	Pulses / Trains	Outcome measures	Results
Shehata et al, 2016 [43]	Pilot randomized	10	80%	Left (M1)	2000 / 20 trains	Primary outcomes: headache frequency (days/month) and severity (VAS). Secondary outcomes: 25-item HDI, HIT-6, and number of acute medications	71.4% had 75% reduction of headache frequency and severity after 4–5 sessions. Significant improvement in the secondary efficacy variable at week 4 (P 0.01 for HDI and P 0.03 for HIT-6). Odds Ratio, 95% CI; 1.25 (0.26-6.07)
Zardouz et al, 2016 [44]	Case series	10	80%	Left (M1)	2000 / 20 trains	NRS, percent reduction in intensity, frequency, and duration of headache.	37.8%, 32.1%, and 31.2% reduction in the intensity, frequency, and duration respectively
Conforto et al, 2014 [45]	Randomized - double blind	10	-	Left DLPFC	1600 / 32 trains	Number of headache days	Number of headache days decreased significantly in the sham group than in the active rTMS group. Odds Ratio, 95% CI; 0.29 (0.01-8.39)
Teo et al, 2014 [46]	Randomized - placebo controlled	10	80%	Right M1	1000 / 20 trains	Headache days, headache index, severity, duration (hours/day), analgesics used	No significant differences between real and sham rTMS. The study was prematurely stopped due to the significant worsening of headache from rTMS.
Misra et al, 2013 [13]	Randomized - controlled double-blind	10	70%	Left frontal cortex	600 / 10 trains	Primary outcomes: reduction in headache frequency and severity (VAS) >50%. Secondary outcome: Improvement in functional disability; rescue medication and adverse events	At 1 month, frequency, VAS score and functional disability improved significantly in rTMS group (P = 0.0001). Odds Ratio, 95% CI; 7.40 (2.95-18.59)
Misra et al, 2012 [47]	Open labeled	10	70%	Left frontal cortex	600 / 10 trains	Migraine frequency, severity, functional disability, MI, rescue medications, and VAS score	Reduced migraine frequency, severity, functional disability, migraine index and rescue medications at all-time points, but the maximum benefit was observed in the first 2 weeks. VAS score improved by >50% in 98% of patients

Teepker, et al, 2010 [48]	Placebo-controlled, blinded	1	-	Vertex	500 / 2 trains	Primary outcomes: migraine attacks. Secondary outcomes: number of headache days, hours with headache, pain intensity and analgesic intake	No significance was observed compared to placebo. (Mann-Whitney U-test, P=0.698).
Brighina et al, 2004 [38]	pilot study	20	90%	Left DLPFC	10 trains	Headache index, frequency and number of abortive medications	Significant reduction of outcome measures during and 4 weeks following treatment. Odds Ratio, 95% CI; 11.00 (0.43-284.30)
M1: motor cortex; DLPFC: Dorsolateral prefrontal cortex; VAS: visual analogue scale, 25-item HDI: Henry Ford Hospital Headache Disability Inventory, HIT-6: Headache Impact Test (HIT-6), NRS: Numerical rating scale, MI: Migraine Index							

Table 1: Comparative analysis of adopted protocols, outcome and results of different rTMS studies.

In a randomized, double-blind, placebo-controlled trial, high-frequency (10 Hz) rTMS delivered to the hot spot of the right abductor digit minimi provided >50% significant reduction in headache frequency and severity with a significant improvement in functional disability when compared to sham treatment [43]. In another study, Teepker, et al. [48] showed that low-frequency rTMS caused non-significant reduction of headache frequency when compared to the sham-treated group. On the contrary, Teo, et al. [46] found that 10 Hz rTMS over M1 is poorly tolerated by chronic migraine patients, with high dropout rate (50%); however, the number of studied subjects was too small for any conclusion. Scalp discomfort and headaches have commonly been reported in rTMS studies, occurring in up to 40% of cases [46].

Data acquired through years of use of TMS suggested its safety. Seizure is rare in patients who use sTMS and is the only adverse event experienced with rTMS to be concerned about, but again the risk is very low [14]. Due to its interaction with some metals, it should be avoided in patients with ferromagnetic implants.

Contemporary Egyptian Experience

In an Egyptian study [43] that compared rTMS to onabotulinumtoxin-A (BoNT-A) injection as preventive therapies for CM on a small-scale sample of 29 Egyptian patients; both treatment modalities have favorable efficacy and safety profiles in chronic migraineurs. It was found that rTMS is of comparable efficacy to BTX-A injection in chronic migraine therapy, but with less sustained effects.

In this study, 14 patients were subjected to 12 rTMS sessions delivered at high frequency (10 Hz) using gure-of-8-shaped

coil over the left motor cortex (MC, M1). The primary efficacy measures were headache frequency (days per month) and severity; secondary measures were 25-item HDI, HIT-6, and number of acute medications. The rTMS protocol in the 14 patients composed of 2000 pulses delivered through 20 trains (10-s apart) of 100 stimuli each at 10 Hz and 80% of motor threshold (MT), 3 days a week, for 1 month. The protocol of this study was adopted according to Brighina et al. [37] assumption, who reported that the motor Intracortical Inhibition (ICI) is significantly lower in migraineurs with subsequent paradoxical increase of Intracortical Facilitation (ICF). They also found that 1-Hz stimulation reduced motor-evoked potential amplitude and ICF in healthy controls, whereas it caused a significant ICF increase in migraineurs and showed that high frequency (10 Hz) stimulation of MC could potentiate ICI and normalize the cortical excitability through increase in short ICI.

The results revealed that about 70% of patients allocated to rTMS arm showed 75% reduction of both headache frequency and severity after 4-5 sessions and this significant improvement was maintained in visit 2 (week 6) and visit 3 (week 8). This study provided an important evidence of “time-locked” effects of rTMS, as authors noticed significantly lower analgesic effect when session duration was shortened. Regarding safety measures; 2/14 patients (14.29%) experienced headache worsening which compelled them to withdraw their consent and one patient (7.14%) had transient tinnitus on the day of session which lasted for few hours and waned the continuation of session

A recent meta-analysis indicated that HF-rTMS using figure-of-8-shaped coil over the left motor cortex is effective for migraine based on 5 randomized controls studies, consisting of 313 migraine patients [49]; yet, several important key areas for further research

are identified which are not only suggested by the findings but also address limitations inherent in the research presented in these studies.

Conclusion

Chronic migraine is a road less travelled by an effective, yet, time-locked rTMS sessions. Though BTX-A can fill a major unmet need for those patients as an effective and safe preventive strategy; yet, there is a need for more non-conventional treatments that can be offered for those with disabling primary headaches who failed to respond adequately to and those with unacceptable side effects or in whom standard preventive treatments are contraindicated.

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