Original Article

Recent Non-Invasive Neuromodulation (NINM) Treatment Trends For Patients With Migraine: A Review

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Abstract

Background- Migraine is a common and debilitating condition. The medications used to prevent migraines can have unpleasant side effects or be useless. In neurology, neuromodulation treatments are becoming more popular. Transcutaneous supraorbital nerve stimulation is useful in the prevention of episodic migraines, whereas stimulation of vagus nerve has promising outcomes in the management of acute migraines. Transcranial stimulation approaches produced a wide range of outcomes, some conflicting.

Aim- To study the effectiveness of non-invasive neuromodulation for patients with migraine.

Method- The data source for this review is done by studying and reviewing articles through databases like PubMed and Google Scholar.

Conclusion- There is significant data which shows that NINM is effective in migraine patients. But the effect is mostly seen in the case of non-invasive stimulation of vagus nerve, transcutaneous supraorbital nerve stimulation and the combination of tSNS with flunarizine.

Keywords: Migraine, Trigeminal nerve stimulation, vagus nerve stimulation, transcranial stimulation & supraorbital nerve stimulation.

INTRODUCTION

Based on the 2010 and 2013 studies of the Global Burden of Disease, migraine affects roughly 14.7 per cent of the general population and is the sixth most common debilitating disorder in the world because of the incapacitating headache and related symptoms [1,2]. Patients frequently report that their migraine headache is unilateral (60%), throbbing (50%), and worsened by physical activity or head movement (90%) [3]. Migraine is commonly preceded by premonitory symptoms such as weariness, decreased attention, and neck stiffness hours or days before the beginning of pain [4]. Migraine is a longstanding neurological condition characterised by reversible neurological and systemic symptoms. Photophobia, phonophobia, cutaneous allodynia, posterior cervical and trapezius regions discomfort or pain and gastrointestinal symptoms such as nausea and emesis are the most common migraine symptoms [3,5]. Chronic migraine, headache happening 15 days per month, causes more impairment and worse productivity than episodic migraine, a headache occurring 15 days per month [6]. The typical length of a migraine is 24 hours and the median time to peak intensity is 12 hours. The duration of a migraine headache can be From 4 to 72 hours in adults. [7].

An effective treatment that has low side effects are desperately needed [8]. Non-invasive neuromodulation (NINM) may be a viable therapy preference. Neuro-modulation is the process of changing nerve activity by sending electrical stimulation to nerves and neural structures [9]. Transcranial direct current stimulation, stimulation of vagus nerve, transcutaneous supraorbital stimulation and transcranial magnetic stimulation are Non-invasive migraine treatments [10]. Need for the study-To review the recent non-invasive neuromodulation treatment strategies for migraine. Our aim is to study is to find the effects of these techniques on the management of migraine.

METHODOLOGY

Several former published articles were studied meticulously, In order to get a better insight into the effectiveness of NINM for the rehabilitation of the patient with migraine.
Databases such as Web of Science, Google Scholar, EMBASE and PubMed were searched for both published and unpublished studies. The last 5-year articles were screened based on inclusion and exclusion criteria to retrieve recent evidence on this topic.

Inclusion Criteria-

A systematic review, meta-analysis, randomized control trial, and case study.
Studies included from the recent year – from 2018 to 2022.
Non-invasive treatment for migraine
Free full-text articles.

Exclusion Criteria

Narrative review, manuscript, pilot study & case reports.
Invasive treatments are excluded.

RESULT

By searching the databases based on search strategy, from the past 5 years 52 articles free full-text articles were found. Based on inclusion and exclusion criteria, 8 articles were selected.

AUTHOR	AIM	Methodology	CONCLUSION
Diener HC et al (2019) [11]	To examine the impact of Non-invasive transcutaneous vagal nerve stimulation (tVNS) on the preventive treatment of migraine	Patients age: 18 to 75. In the past 4 months whichever patient experienced 5-12 migraine days per month. Included. Initially, a run-in period of no treatment contained 4 weeks. Post which 12 weeks of treatment of either sVNS or sham. Finally, open-label period of nVNS for 24-week.	In the intent-to-treat (ITT) population, preventive nVNS therapy for intermittent migraine was not better than other treatments. In treatment-adherent patients, post hoc analysis revealed that nVNS had a substantial effect.
Tassorelli C et al (2018) [12]	To find safety, and tolerability and effect of non-invasive vagus nerve stimulation for the acute treatment of migraine.	Patients age: 18 to 75. Over the last six month who ever had monthly a frequency of 3–8 attacks, with less than 15 head aches/ month With <15 headache days per month over the last 6 months.	This randomised sham-controlled trial reported that as early as 30 minutes and up to 60 minutes post migraine attack the treatmetn is effective. Furthermore it is a safe and tolerable treatment of episodic migraine.
Denise E Chou et al (2019) [13]	Study aimed to find whether external trigeminal nerve stimulation (e-TNS) for acute pain relief during migraine, with or without aura attacks, is safe and efficient or not.	Age: 18–65 years Double-blind Randomized study. A total of 109 participants Subjects may have used any acute medications for migraine but not with in 3 hours of enrolment. 1-hour e-TNS session implemented. A visual analogue scale (VAS) used as outcome	Compared to sham stimulation, one hour of trigeminal nerve stimulation Externally, reduced headache pain. Recommending that it is a safe and effective treatment for acute migraine.
Li Jiang et al (2018) [14]	To find the effectiveness of flunarizine and transcutaneous supraorbital neurostimulation (tSNS) in combination as well as separately.	Age: 18–65 years Inclusion- At least 2 headaches per month. Episodic migraine Patients were enrolled 3 randomized groups. Treatment are A)Flunarizine 5 mg per day, B) tTNS for 20 minutes daily C) combination of both A & B were prescribed for 3 consecutively months.	Without intensifying the side effects. Adding tSNS to flunarizine can enhance migraine prophylaxis therapeutic efficacy. Furthermore, tSNS is an useful and safe migraine treatment alternative for migraineurs who are hesitant to take oral drugs.
Amaal J Starling et al (2018) [15]	The study aimed to find the effect of single pulse transcranial magnetic stimulation (sTMS) as a preventive treatment for migraine.	18 to 65 years of age 4–25 headache days/ month were included. Treatment procedure : preventive (4 pulses two times in a day) and acute (for each attack 3 pulses repeated 3 times)	The study concluded sTMS is well tolerated and may be effective for prevention of migraines.
Azza B Hammad et al (2021) [16]	To find the effect of low-frequency repetitive transcranial magnetic stimulation (rTMS) for migraine	Age : 15 to 55 years rTMS treatment was given for five consecutive days. 2 trains of 500 pulses. Divided by a 1-min interval between. Frequency 1 Hz over vertex.	For migraine with and without aura, rTMS (Low-frequency) is an useful prophylactic treatment.
Mohammad Dawood Rahimi et al (2020) [17]	To test the efficacy of cathodal-tDCS (c-tDCS) in reducing migraine duration, pain frequency and intensity.	Age : 18–57 45 participants 22 sessions of c-tDCS (20min/1000 μa) Duration : 10 weeks Sessions 3 / week initially and One session per week in the final phase.	For the preventative and therapeutic treatment of episodic and chronic migraine the Cathodal-tDCS stimulation on right motor & sensory cortex is useful.
Guoshuai Cai et al (2021) [18]	Systematic Review and Meta-Analysis to find the significance of tDCS on migraine.	Five RCT were included Study which done more than 4 weeks to treat migraine using repeated tDCS. Article included from the first available article up to 2019 December. 18-65 years	4 weeks or longer period of transcranial direct current stimulation (tDCS) is effective in reducing migraine pain severity and duration.

DISCUSSION

This review aimed to understand the effect of non-invasive neuromodulation on patients with migraines. Reviewing of the articles has shown that non-invasive neuromodulation has a significant effect in migraine as it reduces the pain frequency, intensity and duration.

Studies have investigated the effects of different noninvasive neuromodulation methods like vagus nerve stimulation, supraorbital nerve stimulation, external trigeminal nerve stimulation, transcranial magnetic and transcranial direct current stimulation.

1. Non-invasive vagus nerve stimulation

Diener HC et al did a randomised sham-controlled PREMIUM trial in 2019. To investigate the treatment of episodic migraine using vagus nerve stimulation. Total of 477 patients was enrolled, out of which 332 patients were intent-to-treat (ITT) population. Using real or sham nVNS stimulation they were treated three times daily for 12 weeks. The nVNS device creates a 5-kHZ sine wave burst, a low voltage electrical signal lasting for 1 ms. The preventive effects of nVNS were not more significant than sham stimulation (ITT). Treatment gains were greater in patients with aura than in those without and another therapeutic gain.

A study by Tassorelli C et al (2018) in which he did a clinical trial which investigated the efficacy of nVNS as an acute therapy for the treatment of migraine. 248 patients with migraine with episodic migraine were randomised and given nVNS or sham 20 minutes within pain onset. it was found that nVNS is useful and safe for episodic migraine. This acute treatment option showed better results at 30 minutes and 60 minutes as compared to the sham group. But there was no positive result at 120 minutes.

The migraine symptoms may be relieved using nVNS due to the bilateral inhibition happening to parasympathetic function during the application. In addition, few studies reported that this stimulation also inhibits the trigeminovascular connection thereby in the central nervous system extracellular glutamate is reduced. This too alleviates the symptoms of migraine [19- 21]

External trigeminal nerve stimulation

Denise E Chou et al (2017) did an open-labelled pilot study for the acute treatment of migraine. They intended to check the comfort and effect of external trigeminal nerve stimulation. eTNS was given to 30 patients for one hour with a pain intensity of 57.1% and two hours with an intensity of 52.8% and checked. The results were positive. Another randomised sham-controlled trial study by Denise E Chou et al done in 2019. The study was done in acute migraine patients, who may or may not experience aura, to see the safety and effectiveness of eTNS. 106 patients were treated for 1 hour and reported a significant reduction in headache. The treatment was well tolerated. Based on the studies available the anterior cingulate gyrus might be the centre where eTNS could act to reduce migraine headaches [22]

2. Transcutaneous supraorbital nerve stimulation

Li Jiang et al (2018) examined the effectiveness and safety of flunarizine and tSNS in migraine prophylaxis. Three groups were created by randomising 154 patients. For 3 months daily 5mg Flunarizine or 20 minutes of tSNS or a combination of both were implemented. Changes in daily migraine incidence, intensity and medication use were the secondary outcome. The number of incidences that happened on monthly days decreased in all three groups after three months. The combination group showed the better result. The 50 per cent responder rate in the combination therapy was much greater (78.43 per cent) than in flunarizine (46.15 per cent) or tSNS (39.22 per cent) alone. The flunarizine and combination of flunarizine and tSNS had the same number of adverse events. The treatment was safe and effective. Furthermore, a study in 2017 by Paola Di Fiore et al tried to investigate the efficacy of tSNS for prophylaxis of chronic migraine. 23 patients with chronic migraine were treated with tSNS for 20 minutes/day for 4 months. The results showed that tSNS was effective similar to pharmacological prophylaxis of chronic migraine.

Studies were reported that Thalamus is the crucial centre for treating migraine. INHIBITION OF thalamic sensory neurons by cortical spreading depression CSD is a possible mechanism in many effective migraine preventive treatments. [23,24]

Transcranial magnetic stimulation

Amaal J Starling et al (2018) did an open-label prospective study using sTMS for migraine as a preventive treatment. They aimed to find the effectiveness and tolerability of the same.

220 patients were treated for 3 months based on the number of headaches they had per day. The study concluded that sTMS is well tolerated for migraine and might be used as a preventive treatment. Similarly, Azza B Hammad et al conducted a study in 2021, in which they aimed to obtain the effect of low-frequency rTMS for the treatment of migraine (with and without aura). 40 patients were recruited, in that which30 patients were without aura and 10 with aura. Interictally treatment was given for five consecutive days. A significant reduction in migraine pain is noted in terms of its intensity, frequency and duration of attacks. The study concluded that low-frequency rTMS is effective in migraine.

3. Transcranial direct current stimulation

Mohammad Dawood Rahimi et al (2020) did a randomised sham-controlled trial to assess the usefulness of Cathodal tDCS in reducing migraine pain frequency, duration and intensity. The location of the area of stimulation was in the right

primary motor cortex (M1) or sensory cortex (S1) in entities with migraine (episodic or chronic). 45 patients (35 episodic; 10 chronic) were treated for 10 consecutive weeks. Both groups showed a substantial decrease in migraine pain frequency and intensity. Thus, cathodal tDCS is effective for treating migraine. Pain-related plasticity in the brain could be altered using c-tDCS which in teams helps to reduce migraine-related symptoms.

A systematic review and meta-analysis of randomised controlled trials done by Guoshuai Cai et al in 2021. The study aimed to examine the efficacy of tDCS on migraine attacks. Five RCTs with 104 migraine patients were included in the meta-analysis. For a period of four weeks, the treatment was given. Significant pain reduction in intensity and duration was found in active vs sham tDCS. For reducing migraine pain intensity Both anodal and cathodal stimulation was helpful. Typically the electrical changes after stimulation, using one-time tDCS treatment, last one hour only. But repeated and sustained tDCS can produce long-term neural plastic changes in the cortical area of the brain. [25]

As there are sufficient shreds of evidence for the effectiveness of non-invasive neuromodulation for patients with migraine, the treatment has been most effective in the case of nVNS and tSNS and the combination of tSNS and flunarizine. nVNS has a larger population sample size, and the migraine attack intensity is reduced after continuous administration. In the case of tSNS, which alone was effective when given 20 minutes/day for four months, but when it was combined with flunarizine, it had much more effective and was given for 3 months continuously. Furthermore repeated tDCS can also produce neural plastic changes in the cortical brain region and thereby produce a long-term effect in the patient.

CONCLUSION

In conclusion, there is significant data which shows that NINM is effective for patients with migraine. But the effect is primarily seen in the case of nVNS and tSNS and the combination of tSNS and flunarizine can positively affect individuals diagnosed with migraine.

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Competing interests

The authors have declared that no competing interests exist.

Authors’ contributions

Mr Krishna Prasad K M designed the study, following which Mr Stafin Cyriac wrote the first draft of the manuscript. Mr Krishna Prasad K M and Dr Saumya Srivastava revised the manuscript and performed the quality appraisal. All authors read and approved the final manuscript.”

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