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# Repetitive Transcranial Magnetic Stimulation versus Botox Therapy in Chronic Migraine Cases: Pilot Study in a Tertiary Care Centre

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## I. INTRODUCTION

Chronic migraine is the most common type of chronic headache. It affects 1.4%–2.2%of the general population.[1] The 1-year prevalence of chronic migraine is 2.9%.[2] It has a higher impact on health-related quality of life (QoL) due to work day loss and reduced productivity.[3] Cortical spreading depression (CSD) and Trigemino vascular activation are the principal path physiological mechanisms of aura and migraine pain, respectively.[4,5] The chronicity of migraine was also attributed to some changes in cortical excitability due to more impairment of central inhibition.[6] Cortical Neuromodulation of the prefrontal and Motor Cortex (MC) has been shown to be effective in many pain states. Repetitive Tran cranial Magnetic Stimulation (rTMS), with its effect on cortical excitability and could be a potential therapeutic approach for migraine. The current preventive and abortive/acute migraine pharmaceutical treatments may have modest to good efficacy in relieving attacks in migraine patients. But many of the most commonly prescribed preventive and acute treatments have adverse effects that are contraindicated for individuals with cardiovascular issues, kidney issues, pregnancy, or individuals at risk of overuse, addiction, and episodic migraine becoming chronic migraine. Additionally, adverse effects of prescribed pharmaceuticals for migraine may impair the patient from being able to work or engage in social activities decreasing the overall quality of life. A possible novel treatment method that has less severe side effects than commonly prescribed drugs for migraine treatment is rTMS.[7] rTMS has demonstrated efficacy in treating illnesses that have shared pathology and are often co morbid with migraine, including depression and epilepsy.[8] Drug Administration-approved treatment of chronic migraine is Botulinumtoxin-A (BTX-A) injection. There is thus clearly a need for more effective path physiologically targeted treatment strategies. The aim of the current study was to compare the effectiveness and safety of BTX-A, which is being the currently approved standard treatment of chronic headache, to rTMS.

## II. METHODS

This prospective study was conducted on 50 patients who were diagnosed with chronic migraine according to The International Classification of Headache Disorders - third edition-III (beta version). They were recruited from Command hospital (Northern Command) Neurology Department Sep 2018 to May 2020. Patients were randomly assigned tone of two groups; one group received BTX-A (n=25) and the other one received rTMS sessions (n=25). The study was approved by ethical committee CHNC. Written informed consent was obtained from all patients prior to the beginning of the study after a structured interview descriptive the aim and steps of the study.

**Inclusion criteria**

1. Patient with chronic migraine <16 yrs and >70 yrs coming to Headache Clinic at Command Hospital Northern Command from Sep 2018 to March 2020.
2. Chronic Migraine was classified according to ICD beta -3 Criteria Description: Headache occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache.

**Diagnostic criteria**:

A. Headache (migraine-like or tension-type-like1) on ≥15 days/month for >3 months, and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for Migraine without aura and/or criteria B and C for Migraine with aura

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C. On ≥8 days/month for >3 months, fulfilling any of the following: criteria for Migraine

a. Headache has at least two of the following four characteristics:
1) Unilateral location
2) Pulsating quality
3) Moderate or severe pain intensity
4) Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

b. During headache at least one of the following:
1) Nausea and/or vomiting
2) Photophobia and phonophobia

D. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
E. Not better accounted for by another ICHD-3 diagnosis

**Exclusion criteria**
1. Age<16 and > 70 yrs
2. Patients with headache caused by overuse of medication,
3. Psychiatric disorders
4. Symptomatic headache, "Demonstrable structural lesion by Brain Magnetic Resonance Imaging (MRI)," patients who responded to medical treatments, and those with the possibility of lack of coherence during follow-up period. Prior to administration of study treatment, women in childbearing period should have a negative urine pregnancy test and have been using are liable means of contraception.

**Screening phase**

To exclude secondary causes, all the patients were subjected to history taking, clinical assessment, and brain MRI. Thereafter, they were requested to complete a baseline, pretreatment headache diary for 1 month in order to assess for headache days/month; attack frequency, duration, severity, characteristics, precipijtants, and associated symptoms; and number of weekly acute medications. Total 50 patients were recruited.

**Randomization**

Patients were then randomly assigned to one of two groups one group received BTX-A and the other group received rTMS sessions. In BTX-A group (n=25), a total of 155–195 (Botox®) units were injected in a total of 30 sites across seven specific head and neck muscles ± 8 sites (following the pain). BTX-A was diluted with 2 mL of preservative-free normal saline, resulting in a concentration of 5 U/0.1 mL.

In the rTMS group (n=25), 20 trains (10-s apart) of 100 stimuli each delivered at high frequency (10 Hz) and 80% of motor threshold (MT), using figure-of-8-shaped coil over the left MC (M1), were delivered to each patient, 3 days a week, for 1 month. The resting MT for the right abductor pollicis brevis muscle was determined using electromyography. MT intensity was defined as the lowest stimulation intensity that, in 10 trials, induced at least five motor-evoked potentials of at least 50 μV peak-to-peak amplitude. A Magstim Rapid® magnetic stimulator (Magstim Co. Ltd, Whitland, Dyfed, UK) was used, and the maximal stimulator output "peak magnetic field" was 1.2 T. Follow-up visits were scheduled at weeks 4, 8, and12 after baseline visit. In each visit, the headache diary was reviewed. MIDAS Question are were assessed monthly (at weeks4, 8, and 12).HIT-6 was used at weeks 4, 8, and12 after baseline visit

**Outcome measures**

The primary efficacy measures were headache frequency (days/month) and headache severity assessed by MIDAS question are and HIT-6.

**Statistical methods**

Data management was carried out with the Statistical Package for Social Sciences (version 17, SPSS .Simple descriptive analysis in the form of range, mean ± standard deviations, and frequencies (number of cases) were calculated for numerical data, and qualitative data were described using percent distribution. Comparison of BTX-A and rTMS groups in efficacy measures at endpoints using the LOCF was conducted using unpaired Student's t-test, while the differences between means of the variables from same group before and after intervention were assessed using paired t-test. The chi-square test was used for comparison between the two groups of categorical data or frequency of events. P< 0.05 is considered as significant difference.

| Parameters | BTX – A group (n-25) | rTMS Group (n-25) |
|---|---|---|
| Age range (years) | 32±1.2 | 30±1.2 |

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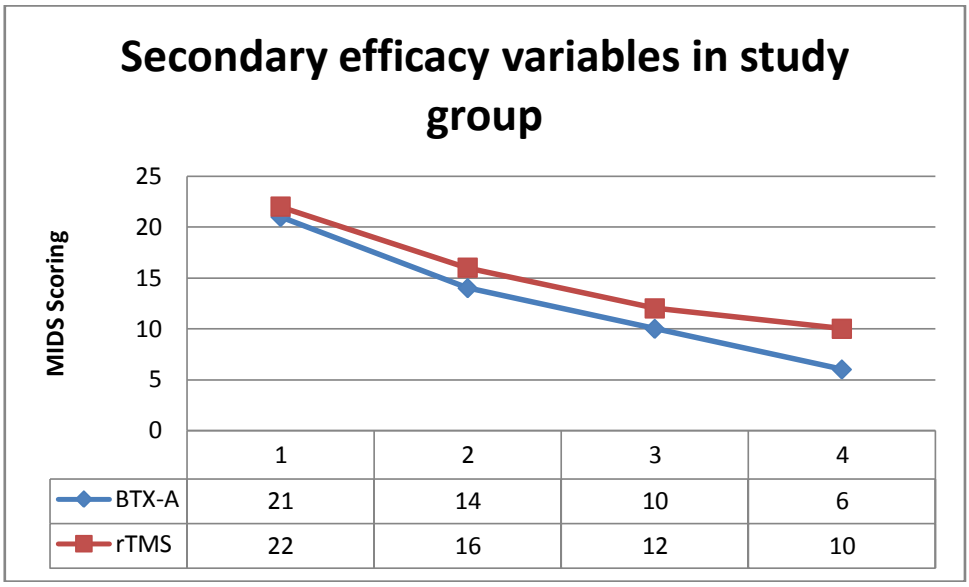
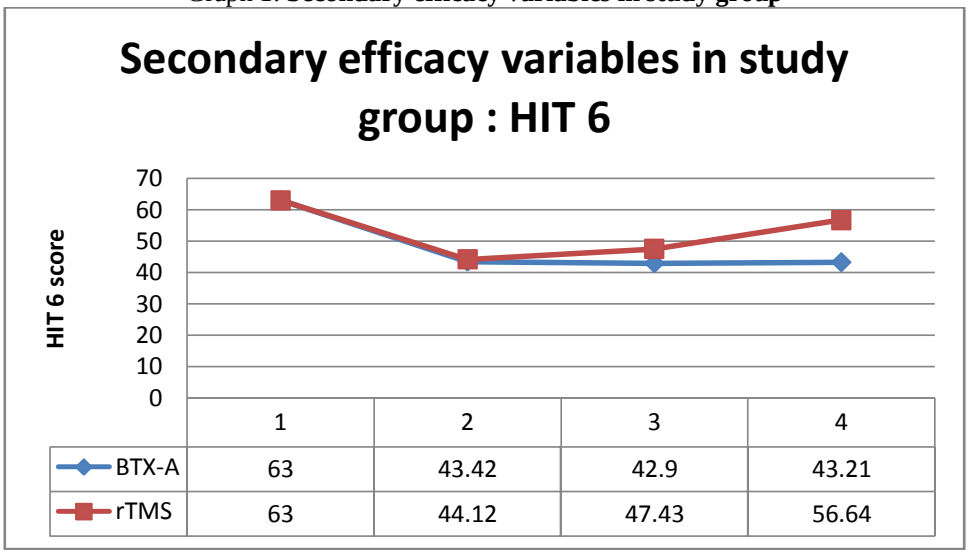
| | | |
|---|---|---|
| Sex : F/M | 15/10 | 14/11 |
| Duration of migraine (Years) | 5.1±2.5 | 5.3±2.3 |
| Duration of chronicity (years) | 2.20±1.36 | 2.30±1.21 |
| Headache days/month | 22±2.1 | 21±2.1 |
| Attack duration(hrs) | 12.1±2.1 | 13.1±2.1 |
| No. of days with acute medication | 10.91±1.2 | 11.91±1.3 |
| HIT-6 | 62.31±4.18 | 62.53±4.15 |

**Table 1- Basic Clinical data of included patients**




Graph 1: **Secondary efficacy variables in study group**




Graph 1: **Secondary efficacy variables in study group HIT6**

## III. RESULTS

A total of 50 patients were allocated to either rTMS sessions or BTX-A injection. Their age ranged from 21 to 60 years (mean age: 32 +_ 5 years). They were 20 males (40%) and 40 females (80%), and the mean duration of migraine was 5.22 ± 3.15 years (ranged from 4 to 11 years).The basic clinical data for both the groups are summarized in Table 1. Intervention in BTX-A arm, the mean injected dose was 176.33 ±16.85 units (Botox®), 16 patients in BTX-A group (66.7%) achieved a 50% reduction in their headache frequency and 18 patients (73.3%) showed 75% reduction in headache severity by the end of third week of injection session. In rTMS group, 17 patients (71.4%) reported 75% reduction of both headache frequency and severity after 4–5 sessions. Headache frequency (headache days per month) and headache severity (VAS) were significantly reduced in the first follow-up visit at fourth week as compared to the month before treatment in both BTX-A and rTMS groups. There was no significant difference between both arms (P= 0.84). This significant improvement was maintained in second visit at eighth week. In the last visits at twelve week, this significant difference was maintained in BTX-A arm whereas in rTMS arm, the difference in headache frequency and severity became no significant.

## IV. DISCUSSION

Studies have supported the use of high-frequency rTMS as an effective treatment for episodic and chronic migraines and it was well tolerated.[9] High-frequency rTMS over the left motor cortex area perform better than sham conditions in reducing headache frequency or severity in few studies reviewed that contained sham conditions.[10] Teo et al did not found difference between treatment and sham conditions. There was no descriptive statistics in the study and each condition only three participants that completed the study.[11] High-frequency rTMS over the motor cortex as compared to sham were more favorable than the previously reported studies in which patients treated with high-frequency rTMS over the left dorsolateral prefrontal cortex experienced notable difficulties in responding to treatment and performed the same or worse than sham conditions (e.g. the studies by Comfort et al. [12] and Granato et al [13].

There is enough evidence that, high-frequency rTMS over the left motor cortex to reduce the number and severity of migraine attacks. Mishra UK et al , in two randomized controlled studies found evidence for high-frequency rTMS over the motor cortex as an effective treatment in episodic and chronic migraine sufferers.[14,15] The findings held not only for improvements in subjective measures of migraine symptomatology (depression, quality of life, severity, etc.) but also for objective biomarkers.[24,25,27,28] This coincided with past research showing that high-frequency rTMS over the motor cortex induced neurological changes in the short-term[16,17]and had the potential to encourage long-term changes in the brain as mentioned by other researchers.[18]In terms of the prescription required to induce the changes, it appeared that as little as three sessions of There is ample evidence that supports the role of rTMS in migraine prevention.

The postulated mechanism of the excitatory effects the connectivity of DLPFC with pain processing centers in the brainstem and thalamus. In a randomized, double-blind, placebo-controlled trial, high-frequency (10 Hz) rTMS delivered to the hot spot of the right abductor digiti minimi provided > 50% significant reduction in headache frequency and severity as compared to sham treatment. There was also significant improvement in functional disability. Teepker et al [19] showed that low-frequency rTMS caused no significant reduction of headache frequency when compared to the sham-treated group. As per Teo et al. there is high dropout rate (50%) with 10 Hz rTMS over M1 and it is poorly tolerated by chronic migraine patients. However, in this study the number of studied subjects was too small for any conclusion. [20] Scalp discomfort and headaches have commonly been reported in rTMS studies, occurring in up to 40% of cases. [21]

In each session of rTMS of 2,000 pulses delivered at 10 Hz over MC was given. This was adopted according to Brighina et al [22]assumption, who reported that the motor ICIis significantly lower in migraineurs with subsequent paradoxical increase of intra cortical facilitation (ICF). They also found that 1-Hz stimulation reduced motor-evoked potential amplitude and ICF in healthy controls, whereas it caused significant increase ICF 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 concept of generalized cortical inter-ictal hyper-excitability, mainly in visual cortex was proposed in migraine is still remain controversial.[23] MT, a parameter used to estimate MC excitability by some authorities was even higher in migraineurs suggesting cortical hypoexcitability.[24] Though, there is no single model

of migraine that explains all of the known features of the disorder; yet, altered functional connectivity between periaqueductal gray and cortical (limbic) centers plays an important role in migraine expression[25]. rTMS has been used in migraine patients to test occipital cortex excitability by measuring phosphene threshold (PT). Minimum intensity of a TMS pulse needed to evoke phosphenes is called PT and it is inversely related to the overall level of visual cortex excitability. [26]

In our study we found that when rTMS sessions were applied on motor area (MC), there are positive results of MC stimulation. However, there are absences of significant benefits on the DLPFC. Other studies also found MC as a more promising target than the DLPFC in patients with chronic migraine. High frequency stimulation of both MC and DLPFC can result in an analgesic benefit. But, their relative mechanisms are different. 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. Stimulation at the DLPF exerts a top-down in hibitory effect along the ascending midbrain–thalamic–cingulate pathway through the descending fibers from the prefrontal cortex, which make it less effective.

The analgesic effects of BoNT were observed 30years ago in patients with Torticollis spasmodic us by Tsui et al.[27] This observation was attributed to the relaxant effects of BoNT. The first evidence for an effect of BoNT on migraine was found in patients who were treated with BoNT for hyper functional lines of the face. Binderet al. in an open-label, nonrandomized study enrolled a total of 106 patients, in which 77 patients were classified as true migraineurs and received prophylactic treatment with on a botulinumtoxin A (Botox®). In this study total of 51% of the patients had complete response and 28%, a partial response. Silberstein et al. in first placebo-controlled, double-blind study in migraine patients (2–8 migraine attacks per month) randomized 123 patients into three groups and treated with placebo, 25 or 75 mouse units (MU) of onabotulinumtoxin A. Patients who were treatment with 25 MU onabotulinumtoxin A was found to be superior to placebo in the reduction of the number of monthly migraine attacks, however no differences was identified between the 75 MU group and the placebo group.

There is significant improvement in headache in both the study arms, in both primary and secondary outcomes. In rTMS group this improvement was recorded earlier after 4–5 sessions. But it wanes faster within 2 weeks after discontinuation of sessions. Whereas in the BTX-A arm, significant improvement was recorded by the end of third week and was maintained till the end of the study period up to 12 weeks. Headset al, have established a long-term maintenance of analgesia induced by high-frequency rTMS patients with chronic facial pain. However, they did not include chronic migraine and they used different protocols, with induction phase and maintenance phase. “Time locked” effects of rTMS is an important evidence of this study. When session duration was shortened there was significantly lower analgesic effect. In the present series, the long-term effects of rTMS is not addressed. The most commonly reported adverse events of rTMS in our patients were headache worsening (14.29%) and transient tinnitus (7.14%); in one study, headache was reported in 42% of participants who received active rTMS and in 33% of whom had sham sessions[28], and this headache was explained by pressing the coil against subjects’ heads for extended periods or by the induced muscle contractions. Most are mild and respond to over-the-counter treatments. Other reported adverse events included pain at the stimulation site, neck pain, muscle aches, dizziness, nausea, tiredness, and tinnitus[29]; however, these adverse events are no more common after real TMS than after sham TMS. To minimize noise exposure from coil discharge and to reduce the risk of transient threshold shifts or hearing loss, all patients was advised to wear earplugs.

Few of limitations of our study should be considered while addressing the results. We have relatively small sample size as compare to other studies. However, since this is a pilot study that provides a bases for feasibility and effectiveness of rTMS in chronic migraine. Other limiting factor is lack of long-term study of rTMS in chronic migraine. A compromised clinical context was adopted to reduce the influence of absence of placebo, It minimize both the conditioning and the learning processes, being crucial mechanisms underlying placebo effect. This was achieved by a structured interview that aimed to clarify the study process and to optimize patients’ expectation especially about the rTMS sessions. To decrease the bias resulting from the interaction between the patient, treating clinician, and treatment environment all follow-up visits were assessed by

independent rater. The long-term efficacy of rTMS is needs to be further study.

## V. CONCLUSION:

Time-locked rTMS sessions are effective in chronic migraine management. However, BTX-A is major unmet need for those patients as an effective and safe preventive strategy. This can be offered for those with disabling primary headaches in whom standard preventive treatments are contraindicated and, who failed to respond adequately and those with unacceptable side effects to conventional treatments.

**Conflict of interest**: Nil

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