EFFICACY AND TOLERABILITY OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION OVER DORSOLATERAL PREFRONTAL CORTEX FOR EPISODIC MIGRAINE PROPHYLAXIS

By

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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December 2022

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Migraine is a disabling primary headache disorder that imposes a substantial burden on the sufferers and society. The role of non-pharmacological therapy such as neuromodulators is increasingly being recognised as a potential therapy for migraine. Repetitive transcranial magnetic stimulation (rTMS) is one of the neuromodulators used in many studies. However, its efficacy in the context of migraine prevention remains unknown, especially in the application on the dorsolateral prefrontal cortex (DLPFC). Our meta-analysis showed a significant reduction in acute medication intake (Mean Difference = 9.78, p =.02, 95%CI = 1.60, 17.96, p =.02) and functional disability (Mean Difference = 8.00, p <.05, 95%CI = 4.21, 11.79).

In this clinical trial, subjects were randomised into rTMS and sham groups. Both groups received five treatment sessions within two weeks and were followed up for three months. Quality of life among the subjects was examined using MIDAS, MSQ v2.1 and EQ-5D questionnaires at baseline and month 3. Physiological changes in transcranial blood flow and serotonin levels were also explored.

Results showed that rTMS over DLPFC was safe with a discontinuation rate of 15.8%. However, the mean number of migraine days, migraine frequency and pain intensity between the two groups did not significantly differ. For the quality of life, the differences in MSQ v2 .1, EQ-5D and MIDAS components were also not significant. Similarly, there were no significant differences observed between the two groups for serotonin concentration and Doppler findings.

In conclusion, this study found that both rTMS and sham similarly reduced mean migraine days with good tolerability. However, the differences in terms of clinical,

biochemical, and neurophysiological markers were statistically insignificant. Current evidence is still not sufficient to recommend the use of rTMS over DLPFC to prevent episodic migraine. Future research should explore different clinical profiles and stimulation protocols.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

KEBERKESANAN DAN KEBOLEH TOLERANSIAN RANGSANGAN MAGNET TRANSKRANIAL BERULANGAN TERHADAP DORSOLATERAL PREFRONTAL KORTEKS SEBAGAI PROFILAKSIS MIGRAIN EPISODIK

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Migrain adalah gangguan sakit kepala primer yang melumpuhkan serta membebankan penghidapnya dan masyarakat. Peranan terapi bukan farmakologi seperti pemodulasi saraf semakin dikenali sebagai salah satu rawatan migrain yang berpotensi. Rangsangan magnet transkranial berulang-ulang (*rTMS*) adalah salah satu pemodulasi saraf yang digunakan dalam banyak kajian. Namun begitu, keberkesanan *rTMS* dalam konteks pencegahan migrain masih belum diketahui, terutamanya dalam aplikasi ke atas korteks dorsolateral prefrontal *(DLPFC).* Analisis meta kami menunjukkan bahawa terdapat pengurangan ketara dalam pengambilan ubat akut (Perbezaan Min = 9.78, p =.02, 95%CI = 1.60, 17.96, p =.02) dan ketidakupayaan untuk berfungsi (Perbezaan Min = 8.00, p <.05, 95%CI = 4.21, 11.79).

Dalam kajian klinikal ini, para subjek dibahagikan kepada kumpulan *rTMS* dan kumpulan palsu secara rawak. Kedua-dua kumpulan menerima lima sesi rawatan dalam tempoh dua minggu dan disusuli selama tiga bulan. Kualiti kehidupan dalam kalangan subjek dikaji menggunakan soal selidik MIDAS, MSQ v2.1 dan EQ-5D pada garis permulaan dan bulan ketiga. Perubahan fisiologi dalam aliran darah transkranial dan paras serotonin turut diteroka.

Keputusan menunjukkan bahawa *rTMS* ke atas *DLPFC* adalah selamat dengan kadar pemberhentian sebanyak 15.8%. Namun bagitu, purata bilangan hari sakit kepala migrain, kekerapan sakit kepala migrain dan keamatan sakit kepala migrain di antara kedua-dua kumpulan tiada perubahan ketara. Bagi kualiti kehidupan, perbezaan dalam komponen-komponen MSQ v2.1, EQ-5D dan MIDAS juga tidak ketara. Begitu juga, tiada perubahan ketara dilihat di antara kedua-dua kumpulan bagi kepekatan serotonin dan dapatan Doppler transkranial.

Kesimpulannya, kajian ini mendapati bahawa *rTMS* dan rawatan palsu kedua-duanya turut sama mengurangkan bilangan hari sakit kepala dengan kadar ketahanan yang baik. Walau bagaimanapun, perbezaan dari segi klinikal, biokimia dan neurofisiologi tidak ketara secara statistik. Bukti semasa masih tidak mencukupi untuk mengesyorkan penggunaan *rTMS* ke atas *DLPFC* bagi mencegah migrain berepisod. Penyelidakan di masa hadapan harus meneroka profil klinikal dan protokol rangsangan yang pelbagai.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

AE	Adverse Events
AHKYK	Abdul Hanif Khan Yusof Khan
AMAR	Anna Misyail Abdul Rashid
ANOVA	Analysis of Variance
CGRP	Calcitonin gene-related peptide
CI	Confidence Interval
cm	Centimetre
cm/s	Centimetre per seconds
DLPFC	Dorsolateral Prefrontal Cortex
EQ-5D	European Quality of Life-5 Dimension
HIT-6	Headache Impact Test – 6
HF-rTMS	High frequency rTMS
JB	Janudin Baharin
MHz	Megahertz
MCA	Middle Cerebral Artery
MD	Migraine Days
MF	Migraine Frequency
MIDAS	Migraine Disability Assessment
MRI	Magnetic Resonance Imaging
MSQ v2.1	Migraine Specific Quality of Life version 2.1
mL	Millilitre
mm	Millimetre
NAM	Nur Afiqah Mohamad
ng/mL	Nanogram per millilitre

NIMS	Nabil Izzaatie Mohamad Safiai
nm	Nanometre
pg/mL	Picogram per millilitre
PCA	Posterior Cerebral Artery
PET	Positron Emission Tomography
PI	Pulsatility Index
PS	Pain Score
RCT	Randomised Controlled Trial
rTMS	Repetitive Transcranial Magnetic Stimulation
SD	Standard Deviations
SR-MA	Systematic Review and Meta-
RoB2	Risk of Bias 2
TCD	Transcranial Doppler Sonography
Vm	Mean flow velocity
WAWS	Wan Aliaa Wan Sulaiman
WCL	Wei Chao Loh
5-HIAA	5-hydroxyindoleacetic acid
5-HT	Serotonin

CHAPTER 1

INTRODUCTION

1.1 Migraine

Migraine is a primary headache disorder that is characterised by a set of symptoms typically a moderate to severe headache which is commonly accompanied by nausea, vomiting, photosensitivity or phonosensitivity (Fitzgerald et al., 2009; Steiner et al., 2019). This neurological disorder predominantly affects women more than men. The global age-standardised prevalence for migraine was estimated to be 18.9% for women and 9.8% for men (Stovner et al., 2018). Even though it does not lead to early death, migraine contributed to about 88.2% of the 46.6 million years lived with disabilities (YLDs) which were attributed to all headache disorders in 2019 (IHME, 2020).

Migraine first debuted in the Global Burden of Disease Study (GBD) in 2000 which ranked 19th (Steiner et al., 2018; WHO, 2001) among the top causes of YLDs. The ranks ascended to 7th in GBD 2010 (Steiner et al., 2013) and then to 6th in GBD 2013 (Steiner et al., 2015). In 2016 and 2019, the ranks had risen to 2nd top causes of YLDs (Steiner et al., 2020; Steiner et al., 2018; Stovner et al., 2018).

Notably, the need to adequately control and manage migraine had advanced their therapeutic aspect (Steiner et al., 2019). Migraine treatment could be grouped into acute treatment or preventive treatment. Even though many pharmacotherapies are available for both acute and preventive treatments, they are only able to relieve migraine attacks and do not significantly improve the condition (Mannix et al., 2016). Acute drug treatment should always be used with caution as it carries the risk of developing medication overuse headache which can be very difficult to manage (Steiner et al., 2019). As for preventive drug treatment, the clinical application was limited due to the medical team and patients' concerns regarding tolerability, adverse effects, regular intake and addiction to the medication (Vécsei et al., 2015).

1.2 Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a type of neuromodulation which is able to induce cortical excitability or inhibit its electrical activity by producing repeated magnetic pulses with short intervals at the cortical areas in a non-invasive way via magnetic stimulation on the scalp (Klomjai et al., 2015). In rTMS, a train of transcranial magnetic stimulation (TMS) pulses is commonly applied at frequencies of 1-50 Hz. Stimulation at a high frequency (5-20 Hz) can

increase cortical excitability, while stimulation at a low frequency (1 Hz) may inhibit cortical excitability (Rossi et al., 2009).

The application of rTMS was first approved in 2008 by US Food and Drug Administration (FDA) for the treatment of major depressive disorder and since then it has been adopted into clinical practice (Hutton, 2014). Earlier studies conducted before the FDA clearance had shown that this neuromodulation is safe with minimal side effects. The most reported side effects were mild headache, neck pain and drowsiness (Lan et al., 2017; Machii et al., 2006). Hence, it is regarded as one of the therapeutic modalities which have huge potential specifically in psychiatric and neurological areas.

Previous research findings had shown that rTMS was efficacious in treating stroke, epilepsy, chronic pain, depression, and anxiety (Du et al., 2019; Fleming et al., 2017; Levkovitz et al., 2015; Rodrigues et al., 2019; Somani & Kar, 2019; Sun et al., 2012). The application of rTMS in headaches and migraine had also been studied and the results also showed positive effects. A study conducted among migraine patients with comorbid depression had shown that rTMS had succeeded in reducing headache frequency and severity of the attack. Besides, the depression rating scale was also improved and rTMS treatment was found to be well-tolerated by the patients (Kumar et al., 2018). A meta-analysis that assessed different types of neuromodulations found that rTMS could effectively reduce the frequency of headache attacks, headache duration, pain intensity of the headache, and number of abortive pills consumed, as well as improve functional ability and depression (Stilling et al., 2019).

1.3 Problem Statement

There has been a huge development in the aspect of pharmaceutical therapy for migraine prevention. Despite that, there is no ideal therapeutic prevention to date. Neuromodulation such as rTMS had been considered to be a highly potential preventive treatment for migraine. The usage of rTMS had been approved by FDA for relieving the acute attack of migraine (*eNeura*). However, research reports on the efficacy of high-frequency rTMS (HF-rTMS) in preventing episodic migraine, especially in its application on the dorsolateral prefrontal cortex (DLPFC) are still scarce. On top of that, the extent of the usefulness of HF-rTMS over DLPFC is still far from being completely understood despite the advancement in the therapeutic areas of migraine prevention.

1.4 Research Objectives

1.4.1 General Objective

The general objective of this research is to evaluate the efficacy of HF-rTMS over DLPFC as a preventive treatment of episodic migraine.

1.4.2 Specific Objectives

The specific objectives of this research are:

1. To evaluate the efficacy of HF-rTMS in preventing migraine among randomised control trials (RCTs) systematically using systematic review and meta-analysis.
2. To assess the safety of HF-rTMS as a preventive treatment of migraine by looking specifically at mean monthly migraine days, mean monthly migraine frequency, and mean monthly pain score.
3. To determine the tolerability of HF-rTMS as a preventive treatment of migraine by looking at the frequency of adverse events and the dropout rate of the subjects.
4. To assess the aspect of health-related quality of life (HRQOL) at pre and post-intervention.
5. To elucidate the utility of serum serotonin concentration as a migraine biomarker in association with HF-rTMS intervention.
6. To explore the physiological features in migraine subjects associated with HF-rTMS intervention using transcranial Doppler (TCD) sonography.

1.5 Null Hypothesis

HF- rTMS over DLPFC is not an effective treatment to prevent episodic migraine.

1.6 Alternative Hypothesis

HF-rTMS over DLPFC is an effective treatment to prevent episodic migraine.

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