

Effectiveness and Tolerability of Repetitive Transcranial Magnetic Stimulation for Preventive Treatment of Episodic Migraine: A Single Centre, Randomised, Double-Blind, Sham-Controlled Phase 2 Trial (Magnet-EM).

Nabil Izzaatie Mohamad Safiai

Universiti Putra Malaysia <https://orcid.org/0000-0003-3635-8322>

Nur Ain Amir

Universiti Putra Malaysia

Hamidon bin Basri

Universiti Putra Malaysia

Liyana Najwa Inche Mat

Universiti Putra Malaysia

Fan Kee Hoo

Universiti Putra Malaysia

Abdul Hanif Khan Yusof Khan

Universiti Putra Malaysia

Wei Chao Loh

Universiti Putra Malaysia

Peck Kee Chia

Universiti Putra Malaysia

Vasudevan Ramachandran

Universiti Putra Malaysia

Hazwan Mat Din

Universiti Putra Malaysia

Intan Nureslyna Samsudin

Universiti Putra Malaysia

Aaron Fernandez

Universiti Putra Malaysia

Mohd Hazmi Mohamed

Universiti Putra Malaysia

Siew Mooi Ching

Universiti Putra Malaysia

Hasnur Zaman Hashim

Avisena Specialist Hospital

Wan Aliaa Wan Sulaiman (✉ waniaaa@upm.edu.my)

Universiti Putra Malaysia <https://orcid.org/0000-0003-4969-0308>

Study protocol

Keywords: Migraine, Repetitive Transcranial Magnetic Stimulation (TMS), Protocol

Posted Date: February 12th, 2020

DOI: <https://doi.org/10.21203/rs.2.23373/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on November 11th, 2020. See the published version at <https://doi.org/10.1186/s13063-020-04832-y>.

Abstract

Background This is a phase II randomised, double-blind, placebo-controlled trial to evaluate the effectiveness and tolerability of repetitive transcranial magnetic stimulation for preventive treatment of episodic migraine among migraine subjects.

Methods Subjects age 18 to 60 years will undergo a baseline evaluation to ascertain the diagnosis of migraine based on International Classification of Headache Disorder 3 rd Edition (ICHD-3). Only those who fulfil the ICHD-3 criteria for episodic migraine and compliant to the headache diary during a month run-in period will be enrolled. A total of 76 subjects will be randomised to receive either transcranial magnetic stimulation or placebo for 5 sessions within 2 weeks duration. Follow up sessions will be conducted monthly for three consecutive months. Prior to treatment, subjects will be required to fill up questionnaires and undergo few procedures such as electroencephalography, transcranial doppler ultrasound and biochemical analysis for serum serotonin, serum calcitonin-gene related peptide and serum beta-endorphin. These procedures will be repeated post-treatment during their last visit. The primary outcome measure of this study is the difference in mean monthly migraine days at baseline and at month 1, 2 and 3 after treatment sessions.

Discussion Following evidence from previous studies showing restoration of dorsolateral prefrontal cortex (DLPFC) activation to near normal level, the rTMS intervention will target left DLPFC in this study. Meanwhile, in terms of treatment frequency, the least number of sessions reported which proved to be effective in treating migraine was three session of rTMS given in alternate days. Hence, for this study, an intermediate duration of treatment sessions is selected. It is set to five treatment sessions given within 2 weeks duration.

Introduction

Background and rationale {6a}

Migraine is a common neurological problem encompassing about 11% global prevalence around the globe (1). One-year prevalence for migraine in Asia-Pacific Region is 9.1% (1.5-22.8%) which is relatively consistent throughout the region (2). Migraine is a neurological problem most commonly begins at young age during the first three decades of life and peaks at puberty which are around the age of 12 and 15 for boys and girls respectively (3). Many previous studies had showed the predominance of women in migraine. Studies had suggested migraine basically caused by genetic factors. First-degree relatives or family suffers from migraine with aura (MA) are prone to inherit the genetic and hold almost four-fold enhancement risk to suffers while for migraine without aura (MO) have two-fold increased risk (4).

Transcranial magnetic stimulation (TMS), is a non-invasive neuromodulation procedure for migraineurs and previous studies proved it to be safe and effective option of a non-pharmacological migraine treatment. TMS is given using a device that delivers a predetermined level of magnetic pulses to the scalp. In repetitive TMS (rTMS), a train of TMS pulses, like those given in single pulse TMS (sTMS), are

applied at frequencies of 1-50 Hz. Low frequency rTMS (1 Hz) has been demonstrated to inhibit cortical excitability, whereas high-frequency stimulation (5-20 Hz) may lead to an increase in cortical excitability (5).

Based on the theory that repetitive TMS alters brain excitability and neurotransmitter activity, several studies that examined TMS as a preventive migraine treatment and some had shown positive results. However, there are many uncertainties regarding the extend of efficacy of TMS specifically the information to identify the group of patients that will benefit from TMS (6). Therefore, its role as an effective and safe non-pharmacological treatment for migraine need to be further determined in different population.

Objectives {7}

The main objective of this study is to evaluate the efficacy of rTMS in the adjunctive treatment of episodic migraine subjects. We hypothesize that rTMS is effective as an adjunctive treatment of episodic migraine.

Trial design {8}

This study is a single centre, randomized, double-blind trial comparing sham and active transcranial magnetic stimulation. This trial is currently ongoing in Headache Research Clinic, Neurophysiology Laboratory, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia. This study has been approved by local ethics committee and review board (Universiti Putra Malaysia Ethics Committee for Human Research (JKEUPM-2018-397)).

Methods: Participants, Interventions And Outcomes

Study setting {9}

This trial is currently undergoing in Headache Research Clinic, Neurophysiology Laboratory in Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Seri Kembangan, Selangor, Malaysia.

Eligibility criteria {10}

The criteria are:

Inclusion Criteria

1. Males or females aged 18 to 60 years of age.

2. Subjects fulfilling criteria for episodic migraine as per the Third Edition of The International Headache Society (ICHD-3) for at least 1 year.
3. Frequency of migraine attacks 2-8 times per month with less than 15 headache days per month for at least 3 months prior to screening.
4. Demonstrated compliance with the headache diary during the run-in period by entry of headache data on a minimum of 24/30 days (80% compliance).
5. A signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study including any known and potential risks and available alternative treatments.

Exclusion criteria

1. Patients with previous history of rTMS treatment.
2. Onset of headache at more than 50-year-old.
3. Headache with red flags symptoms that may suggest organic secondary headaches.
4. Pregnant or lactating women.
5. Patients with contraindications to TMS such as metallic implant and pacemaker based on the Screening 13-item Questionnaire for rTMS candidate.
6. Patients with medical conditions such severe hypertension, infections, malignancy, cardiovascular and cerebrovascular disease, epilepsy, degenerative central nervous system diseases, renal failure, hepatic failure, bleeding diathesis and serious mental illness.

Who will take informed consent? {26a}

Principal investigator and any research members who had been delegated the task to request informed consent from the participants by the principal investigator. The researchers must have a valid Good Clinical Practice Certificate (GCP) awarded by National Pharmaceutical Regulatory Authorities (Malaysia).

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Any collection of data or biological specimens for future use will need to request new ethical approval from institutional review board and new consent from participants.

Interventions

Explanation for the choice of comparators {6b}

The sham stimulation will be given using a sham coil in the same manner as rTMS. The sham coil is a Magstim Rapid-2 (Whitland, Walsh, UK), 70mm Double Air Film Sham Coil. The Magstim Air Film sham coil is identical in all but stimulation output. Patients assigned to sham coil will undergo similar procedures as patients receiving rTMS coil and will also receive the same total sessions.

Intervention description {11a}

The magnetic stimulation will be given using Magstim Rapid-2 (Whitland, Walsh, UK), 70mm Double Air Film Coil. The magnetic stimulator will be placed antero-posteriorly parallel to midline on the left dorsolateral prefrontal cortex (7) corresponding to the hot spot of the right abductor digiti minimi (7 cm lateral and 5 cm anterior to the inter- aural line). The motor threshold will be determined prior to the first session of the intervention at the hot spot of the right abductor digiti minimi. Motor threshold is defined as the minimum stimulus intensity able to elicit 5 or more motor-evoked potentials of 50 IV out of 10 consecutive stimuli.

Only 80 % of the motor threshold will be used. Each session of rTMS will consist of 2000 pulses given in 40 cycles. Each cycle duration is 2.5 seconds consisting of 50 pulses at 20 Hz with intertrain interval of 25 seconds. The total of five sessions are designed to be delivered within two weeks in which the first three sessions will be done consecutively in the first week and the last two sessions will be given consecutively in the second week. In total, ten-thousands cumulative pulses will be delivered to

participants in the span of two weeks. Any adverse events during the two weeks stimulation period and four weeks post treatment will be monitored.

Criteria for discontinuing or modifying allocated interventions {11b}

There will be no modification allowed to the allocated intervention in this trial. The criteria for discontinuing allocated interventions are:

1. Pregnancy
2. Subject's withdrawal

However, any data collected up to the time of discontinuation will still be used for the study.

Strategies to improve adherence to interventions {11c}

Methods to motivate compliance (check-ups, pamphlets, education) and monitor compliance will be used. Every patient will be asked to choose the treatment sessions and schedule appointment depends on their availability and also the availability of the provided time slot for the sessions and appointments (to prevent redundancy with another participants). They will be reminded regarding the appointments through messages from the member of the research team.

Relevant concomitant care permitted or prohibited during the trial {11d}

Any concomitant care either for migraine or any other illnesses are allowed throughout this study.

Provisions for post-trial care {30}

All patients are entitled for medical insurance coverage in this study.

Outcomes {12}

The primary outcome measure of this study is the changes in mean monthly migraine days during a month before randomization and month 1, 2 and 3 after treatment sessions. The secondary outcome measures are differences in mean monthly migraine attacks, proportion of subjects with at least a 50% reduction from baseline in mean monthly migraine days, change from baseline in mean monthly pain intensity of migraine attacks, frequency and severity of adverse events in response to rTMS, the pattern changes in electroencephalography (EEG) and transcranial Doppler sonography (TCD) at baseline and 3 months after the last treatment session, serum serotonin, serum calcitonin gene-related peptide (CGRP) and serum beta-endorphin level changes at baseline and 3 months after the last treatment session, Migraine Specific Questionnaire version 2 (MSQv2.1) at baseline and 3 months after the last treatment session, Depression Anxiety and Stress 21 Scale (DASS21) at baseline and 3 months after the last treatment session, European Quality of Life 5 Dimension (EQ-5D) at baseline and 3 months after the last treatment session, Migraine Disability Index (MIDAS) at baseline and 3 months after the last treatment session, Pittsburgh Sleep Quality Index (PSQI) at baseline and 3 months after the last treatment session, Global Physical Activity Questionnaire (GPAQ) at baseline and 3 months after the last treatment session, Food Frequency Questionnaires (FFQ) at baseline and satisfaction measures of efficacy, tolerability, safety and expectations of r-TMS among the participants at 3 months after the last treatment session.

Participant timeline {13}

Participants will be screened for eligibility during their first visit. Their history will be taken during screening visit to establish the diagnosis according to ICHD-3 beta version. If they are eligible, a diary will be given to them to record the frequency of their migraine attack in a month. Participants will receive rTMS treatment for a total of 5 sessions days within 2 weeks. Only one treatment session will be given per day. Participants will receive 3 consecutive sessions per week in the 1st week and 2 consecutive sessions in the 2nd week. This means that the participants are required to present themselves to the

headache research clinic 5 times within 2 weeks for the treatment phase. The follow-ups will be conducted after 1 month, 2 months and 3 months as shown in Figure 1.

Table 1 Schedule of study

STUDY VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Check eligibility	X	X								
Questionnaires			X						X	
Study intervention			X	X	X	X	X			
Randomisation			X							
Laboratory test			X						X	
Headache Diary	X						X	X	X	
AE monitoring		X	X	X	X	X	X	X	X	
EEG		X							X	
TCD	X								X	

Table 1: Questionnaires included are MIDAS, EQ5D, PSQI, MSQv2.1, GPAQ, DASS21, FFQ and satisfaction measures of efficacy, tolerability, safety and expectations of r-TMS. Laboratory test included are measurement of serum serotonin level, serum beta endorphin level and serum CGRP level. AE = Adverse events, EEG = Electroencephalography, TCD = Transcranial Doppler, V = Visit.

Sample size {14}

A statistical analysis was calculated according to hypothesis testing method, which $\alpha=0.05$ and power = 80%. According to previous literature, the main outcome, the monthly headache days in rTMS treatment

group improved to 5.2 ± 4.9 meanwhile the monthly headache days in sham treatment group improved to 8.9 ± 6.6 . Thus, the initial sample size calculation is estimated based on the following formula. Each group need at least 38 participants (assuming 30% attrition rate), therefore, 76 patients will be enrolled in this study.

Recruitment {15}

Participants are recruited from nearby community and they are encouraged to come to our Headache Research Clinic for initial screening appointment. During initial screening appointment, participants will be informed regarding the details of the study. Medical history will be taken from the participants to establish the diagnosis of their headache. Only participants fit the criteria for migraine with aura and migraine without aura according to the third edition of International Classification of Headache Disorders (ICHD- 3 beta) will be included in this study.

Assignment of interventions: allocation

Sequence generation {16a}

A randomization sequence will be generated with the help of online research randomizer (randomizer.org) by an external member, who is not directly involved in the study. The final code is only known to the external member and the document will be stored in a secure locked safe by the external member. The key coding to the allocation will be revealed by the external member at the completion of the study.

Concealment mechanism {16b}

To have a strict implementation of the generated random sequence, the concealed allocation is achieved using sequentially numbered, opaque and sealed envelopes (SNOSEs) prepared by an external member. An aluminum foil is kept inside the envelope to prevent any chances of deciphering. The envelopes will only contain the label of the devices which are "Treatment A" or "Treatment B". This label will be put onto

the sham coil and the rTMS coil by the same external member. This procedure prevents any influences either from the patients or the researchers towards the randomization process.

Implementation {16c}

The study number will be assigned at the point of enrollment after the patient signed and dated the informed consent. In this study, the study number is the same as the randomization number, however, the point of randomization is done directly before the first treatment session. The principal investigator and the blinded team may assign the participants to the intervention according to the treatment label inside the envelope.

Assignment of interventions: Blinding

Who will be blinded {17a}

Participants, principal investigator and blinded team members including the outcome assessor are blinded to the assignment of the intervention. Data analyst and external members who will not directly involved into the study will be in the unblinded group.

Procedure for unblinding if needed {17b}

If any adverse events or pregnancy occurs for which knowledge of the identity of the test coil is necessary to manage the subject's condition, the sealed emergency code key for that subject may be unblinded and the test coil identified immediately. The investigator will call the external member whom generate the randomization sequence and keep it in a locked safe and request for the emergency code key for that subject to be broken to identify the test coil.

Data collection and management

Plans for assessment and collection of outcomes {18a}

The training sessions are done in a few sessions to ensure all the researchers know the trial procedures. Principal investigator which is a consultant neurologist had trained and assess each researcher who had been delegated to do the tasks. In addition, the questionnaires use in this trial are reliable and had been validated by other studies.

Plans to promote participant retention and complete follow-up {18b}

Participants will receive text messages and phone calls for scheduled visits. At least, two written attempts and one phone call will be made to follow up patients before a patient is defined as lost to follow up.

Data management {19}

Data management will be conducted using appropriate database and validation programmes. Accurate and reliable data collection will be assured by verification and cross-check of 100% of the CRFs against the investigator's records (source document verification). The data collected will be entered into a computer database and subject to quality assurance procedures as dictated by Standard Operating Procedures of Malaysian GCP.

1. Data entry

All the data will be recorded into the computer programs using the Microsoft Excel 2013.

2. Data validation and Data Query

Data will be abstracted retrospectively from computerized medical records by a database query for the identified patients. These data will be validated and augmented by abstracting data from the patients' paper records.

3. Clean File and Database Lock

The missing data will be managed by running standard data-cleaning reports, which identify missing values or missing records. Once all the data collected during the visits have been transferred and captured in the database, cleaning, reconciliation, and verification activities will be performed for smooth database lock.

Relevant bodies such as the institutional ethics committee (JKEUPM) and sponsor (RMC UPM) would also have access to the study data.

Confidentiality {27}

All the information obtained in this study will be kept and handled in a confidential manner, in accordance with applicable laws and/or regulations. Subjects must be identified only by their assigned identification number and initial on all CRFs and other records and documents. When publishing or presenting the study results, participant's identity will not be revealed without his/her expressed consent. Individuals involved in this study and qualified monitors and auditors, the sponsor (UPM) or its affiliates and governmental or regulatory authorities may inspect and copy the medical records, where appropriate and necessary. Since this study will not reveal individual results, all the results will be kept confidential unless the subjects requested the result personally.

Biospecimens of the study participants may be tested in local university laboratories, however the biospecimens will be coded and information that can identify the participants will be removed.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

In this study, about 4-5ml blood samples will be taken from patients to measure serotonin level, calcitonin gene related peptide level and beta endorphin level in the serum during baseline and post-treatment. Blood will be taken from antecubital vein of participants and will be collected in a serum separator blood tube.

The centrifugation process should be commenced within relevant time period and should not exceed more than 3 hours to ensure accurate reading of biochemical parameter. The extracted samples will be stored in a -80°C freezer until the samples are ready to be analysed. The biochemical parameters will be analyzed using commercial ELISA kit according to the manufacturer protocol.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Data analysis will be performed by a medical statistician who is blinded to the entire allocation and treatment process. SPSS statistical software package vision 22.0 will be used to assed the study data. The intention-to-treat principle will be used for all efficacy analyses. Two-tailed analyses will be performed, with significant level is set at 0.05.

Demographic characteristics and baseline measurement of the variables of each group will be summarized. Characteristics of the patients in each of the groups at baseline will be compared using independent T-test or Mann Whitney test for continuous variables, depending on the normality test for the variable. Chi-square or Fisher's exact will be used to compare categorical variables between the groups.

The mean change of the monthly migraine days is the primary outcome measure of this study. For normality assessment, Kolmogorov-Smirnov test and graphical approach through histogram with normal curve will be used. Continuous variables will present as means \pm SDs if they are normally distributed or

as median with IQRs if they are skewed. For multivariate analysis, repeated measure Analysis of Variance (ANOVA) will be used to compare between subject effects (treatment effect), within subject effect (time effect) and within-between subject effects (treatment-time effect) comparisons. Assumptions for repeated measure ANOVA will be checked, which are assumption of compound symmetry, normality of residuals and homogeneity of variance. Assumption of compound symmetry will be assessed through Mauchly's test of sphericity, with normality of residuals will be examined through histogram with overlaid normal curve of residuals, while homogeneity of variance will be assessed through Levene's test. If one of the assumptions is not met, proper remedial measure will be taken including extreme outliers' elimination and data transformation.

The secondary outcome measures include the mean change of monthly migraine attacks, proportion of subjects with at least a 50% reduction, mean change of monthly pain intensity of migraine attacks, frequency and severity of adverse events in response to rTMS, mean changes in EEG and TCD, from baseline to endpoints in the study. All secondary outcome measures will be analyzed following the same method for primary outcome measure analysis.

Interim analyses {21b}

There will be no interim analysis in this study.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Comparison between subject effects (treatment effect), within subject effect (time effect) and within-between subject effects (treatment-time effect) will be done using ANOVA.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

As for missing data management, the last observation carries forward method will be used for the primary outcome.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Not Available.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

Not available.

Composition of the data monitoring committee, its role and reporting structure {21a}

The progress report will be sent bi-annually to the sponsor and ethics committee. The data monitoring committee from the sponsor will monitor the trial annually.

Adverse event reporting and harms {22}

Information about all serious adverse events will be recorded on the Serious Adverse Event (SAE) Page of the case report form. All events documented in the SAE Form must be reported within 24 hours to the ethics committee and sponsor by fax. The investigator should not wait to receive additional information to fully document the SAE before notifying ethic committee. A fax SAE form detailing relevant aspects of the SAE in question should follow telephone report of SAE. The investigator should also comply with the applicable regulatory requirements related to the reporting of unexpected serious reactions to the regulatory authorities.

Where applicable, information from relevant from medical records and autopsy reports should be obtained. Any death or congenital abnormality, if brought to the attention of the investigator within 6 months after cessation of study treatment, whether considered treatment related or not, should be reported to institutional ethics committee.

Frequency and plans for auditing trial conduct {23}

The ethics committee (JKEUPM) will do the auditing process annually.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any amendment will be sent to ethics committee (JKEUPM) again for seeking approval. Any approved amendment will only be commenced after approval from ethics committee. Any changes in eligibility criteria will be informed to the participants during re-consent procedure using latest patient information sheet and consent form.

Dissemination plans {31a}

The study outcome will be disseminated through peer-reviewed publications.

Discussion

Many researchers had conducted rTMS trials to determine the efficacy of rTMS as treatment of both chronic and episodic migraine. In a systematic review done by (8) , three studies were graded as high quality study with low risk of overall bias. (7) did a parallel group, randomised, double-blind clinical trial on 11 chronic migraine patients. In this study, left dorsolateral pre-frontal cortex (DLPFC) which was localized anatomically at 5cm anterior to the FDI motor hotspot was targeted. The participants received 12 sessions of therapy on alternate days for few weeks. A total of 400 pulses was delivered each session consisting of 10 cycles of 40 pulses with intertrain interval (9) of 30s. The frequency of rTMS was delivered at 20 Hz with stimulation intensity was at 90% of resting motor threshold (RMT). The result of

the study showed rTMS was safe with no reported side effects and effective to reduce migraine attack, number of abortive pills and headache index.

Another study was a single centre, randomised, sham-controlled, double-blind clinical trial done by (10). In the study, 100 episodic migraine patients were given only three sessions of rTMS on alternate days. The frequency of rTMS was set at 10 Hz and the stimulation intensity was 70% RMT of abductor digiti minimi muscle. Each session consisted of 60 pulses given in 10 cycles with intertrain interval of 45 seconds. In contrast with the previous study, in this study they targeted left motor cortex. The primary outcome of this study had shown that the headache frequency reduction was more in rTMS group compared to sham group. In term of safety, there were no reported side effects in sham group. In rTMS group, only one patient had complained of drowsiness for 12 hours and fortunately had no drowsiness when rTMS treatment was repeated after 1 month.

Meanwhile, in 2014, (11) did a single centre, randomised, double-blind, parallel-group study on chronic migraine. This study targeted left DPFLC at higher stimulation intensity (100% RMT), with longer duration 23 sessions of rTMS delivered over eight weeks. On top of that, more pulses were delivered each session compared to the last two study (total number of 1600 pulses, 30 s ITI) at a lower frequency of 10 Hz. In contrast with the study done by Brighina et. al, the result from this study showed that rTMS did not effectively reduced headache days in chronic migraine patients. Apart from that, the reported side effects also were more compared to the previous two studies. One patient had hypesthesia in the region of her ophthalmic division of left trigeminal nerve (V1). Seventy-eight percent of patients in active group had pain at the site of treatment or onset of headache or worsening of headache during rTMS treatment, meanwhile in sham group, only 33% reported the same complaint. Sleepiness was reported in 7 out of 9 subjects in both groups.

Apart from Brighina et. al, tremendous researches studied about depression had targeted DLPFC due to restoration of DLPFC activation to quite the normal level as shown using PET imaging and magnetic resonance. Considering this evidence, we decided to target DLPFC in our study.

TMS is widely considered to be a safe technique, however, has induced brief seizures in a small number of individuals worldwide. Since 1998, seizures due to TMS have occurred, but mostly in studies operating outside the safe limits previously defined. Incidents of seizures in studies operating within the safe parameters occurred in subjects using pro-epileptogenic medication. Considering the very large number of subjects who have participated in TMS studies since 1998 and the small number of seizures, the risk of TMS inducing seizures is considered to be very low (5).

In recent systematic review that included 93 placebo-controlled RCTs, (9) reported that headache or discomfort at stimulation site was the most commonly reported in both active treatment and placebo group (19.7% vs 10.1% respectively). The second most commonly reported adverse effects was dizziness accounting about 1.8% in placebo group and 2.8% in active TMS group.

Following the updated guideline article for the use of transcranial magnetic stimulation intended for research and clinical settings (5), we developed a study protocol to treat episodic migraine in adjunctive treatment setting. In this study, we set the rTMS stimulation intensity at 80% RMT. A total of 2000 pulses given in 40 trains will be delivered at 20 Hz frequency in every session. In each train, 50 pulses will be delivered in a span of 2.5s followed by intertrain interval of 25s.

After considering the feasibility of study and other factors such as outpatient setting, local culture and community recruitment, we set the treatment sessions to only five sessions given in alternate weeks. The first three consecutive sessions will be in the first week and the last two consecutive sessions will be in the second week. We would like to determine whether a low number of sessions given in a higher frequency would be able to ameliorate episodic migraine or not.

Trial Status

This is version 4 protocol dated 01/10/2019. The recruitment had begun on 15th April 2019 and approximate date of last recruitment would be on 30th June 2020.

Abbreviations

CGRP	Calcitonin Gene Related Peptide
DASS21	Depression Anxiety Stress Scale 21
DLPFC	Dorsolateral Pre-frontal Cortex
EEG	Electroencephalography
EQ-5D	European Quality-of- Life 5 Dimension Questionnaire
FFQ	Food Frequency Questionnaire
GCP	Good Clinical Practice
GPAQ	Global Physical Activity Questionnaire
MIDAS	Migraine Disability Assessment
MSQ 2.1	Migraine Specific Quality of Life Questionnaire Version 2.1
PSQI	Pittsburgh Sleep Quality Index
rTMS	Repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Events
TCD	Transcranial Doppler

Declarations

Acknowledgements

We would like to express our thanks for Professor Dr Lye Mun San, for his help in sample size estimation and advice in study design. We appreciate Mrs Musmarlina Omar, Mrs Nur Izzati Hasan and Mr Muhammad Izzuddin from Neurophysiology Unit, Department of Medicine, Universiti Putra Malaysia for their technical and administrative support.

This trial was supported financially by Research Management Centre Universiti Putra Malaysia under Putra Grant (GPB/2017/9585500).

Authors' contributions {31b}

NIMS, NAA, WAWS, INS, LNIM, HB participated in the conception and design of the trial, in plans for the analysis of the data, and in drafting the manuscript. AF, RV, HFK, CSM, MHM, HMD participated in the conception and design of the trial, in plans for the analysis of the data, and in drafting the manuscript. AHKYK, LWC, CPK and HZH participated in the conception and design of the trial, in plans for the analysis of the data, and in drafting the manuscript.

All authors read and approved the final manuscript.

Funding {4}

This work is supported by Research Management Centre, Universiti Putra Malaysia (Grant Number 9585500). The sponsor had reviewed and approved this study protocol. Sponsor will also implement quality control and quality assurance throughout the study and monitoring the progress of the research trial. Sponsor will also review the recorded data, the data interpretation and the analysis of data to ensure the researchers comply to the study protocol.

Availability of data and materials {29}

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate {24}

This study has been approved by local ethics committee and review board (Universiti Putra Malaysia Ethics Committee for Human Research (JKEUPM-2018-397)). Informed consent will be obtained from all participants prior to participation in this study.

Consent for publication {32}

Not applicable.

Competing interests {28}

The authors declare that they have no competing interests.

Author details

Nabil Izzaatie Mohamad Safiai¹, Nur Ain Amir¹, Hamidon bin Basri¹, Liyana Najwa Inche Mat¹, Hoo Fan Kee¹, Abdul Hanif Khan Yusof Khan¹, Loh Wei Chao¹, Chia Peck Kee¹, Ramachandran Vasudevan², Hazwan Mat Din², Intan Nureslyna Samsudin³, Aaron Fernandez⁴, Mohd Hazmi Mohamed⁵, Ching Siew Mooi⁶, Hasnur Zaman Hashim⁷, *Wan Aliaa Wan Sulaiman^{1,2}.

Affiliation

1. Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.
2. Malaysian Research Institute on Ageing, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.
3. Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.
4. Department of Psychiatry, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.
5. Department of Surgery, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.
6. Department of Family Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.
7. Avisena Specialist Hospital, Medical Department, Jalan Ikhtisas, Seksyen 14, 40000 Shah Alam, Selangor, Malaysia.

Corresponding Author

Correspondence to Wan Aliaa Wan Sulaiman

Authors' information (optional)

References

1. Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia : an international journal of headache*. 2007;27(3):193-210.
2. Peng KP, Wang SJ. Epidemiology of Headache Disorders In The Asia-pacific Region. *Headache*. 2014;54, 610-8.

3. Goadsby PJ, Lipton RB, Ferrari MD. Migraine – Current Understanding And Treatment. *New England Journal of Medicine*. 2002;346:257–70.
4. Kowalska M, Prendecki M, Kozubski W, Lianeri M, Dorszewska J. Molecular factors in migraine. *Oncotarget*. 2016;7(31):50708-18.
5. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMSCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. 2009;120(12):2008-39.
6. Lan L, Zhang X, Li X, Rong X, Peng Y. The efficacy of transcranial magnetic stimulation on migraine: a meta-analysis of randomized controlled trials. *J Headache Pain*. 2017;18(1):86.
7. Brighina F, Piazza A, Vitello G, Aloisio A, Palermo A, Daniele O, et al. rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. *J Neurol Sci*. 2004;227(1):67-71.
8. Stilling JM, Monchi O, Amoozegar F, Debert CT. Transcranial Magnetic and Direct Current Stimulation (TMS/tDCS) for the Treatment of Headache: A Systematic Review. *Headache*. 2019;59(3):339-57.
9. Zis P, Shafique F, Hadjivassiliou M, Blackburn D, Venneri A, Iliodromiti S, et al. Safety, Tolerability, and Nocebo Phenomena During Transcranial Magnetic Stimulation: A Systematic Review and Meta-Analysis of Placebo-Controlled Clinical Trials. *Neuromodulation*. 2019.
10. Misra UK, Kalita J, Bhoi SK. High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: a randomized, placebo-controlled study. *Journal of neurology*. 2013;260(11):2793-801.
11. Conforto AB, Amaro E, Jr., Goncalves AL, Mercante JP, Guendler VZ, Ferreira JR, et al. Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. *Cephalgia*. 2014;34(6):464-72.

Figures

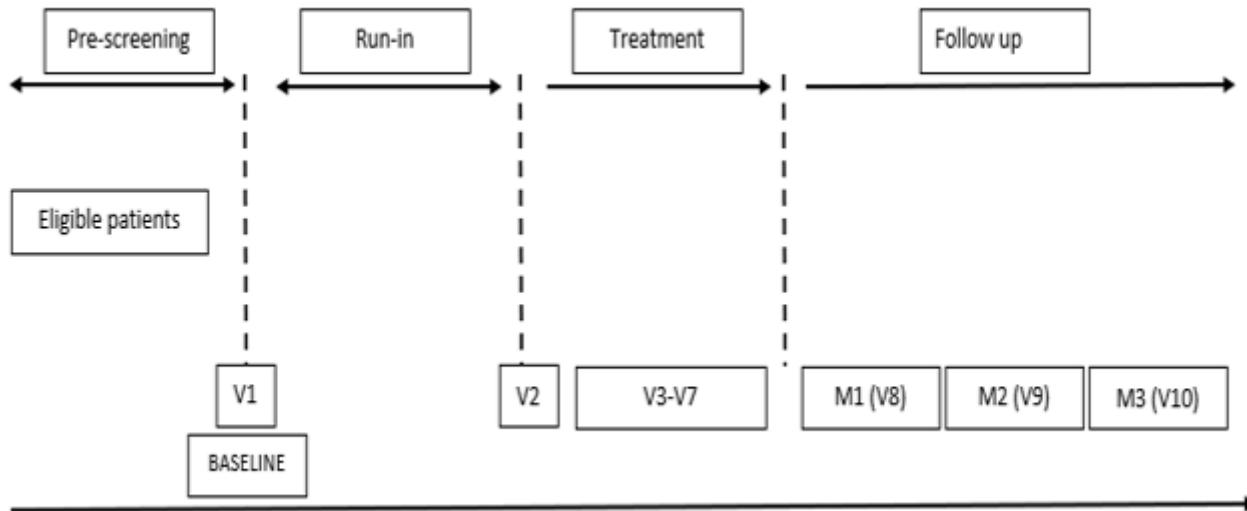


Figure 1

Participants timeline. V = visit, M = month.