DATE: 11-NOVEMBER-2020

TITLE OF STUDY:

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

Brief Title: Transcranial Magnetic Stimulation in Episodic Migraine (Magnet-EM)

NCT NUMBER: NCT03556722

SPONSOR:

Research Management Centre (RMC) Universiti Putra Malaysia

CLINICAL PHASE: 2

INVESTIGATORS:

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OBJECTIVES:

- Primary objective:

To evaluate the efficacy an of r-TMS in the adjunctive treatment of episodic migraine subjects

- Secondary objectives:

1. To evaluate the safety of r-TMS in the treatment of migraine.
2. To identify the factors that predicts good responses to TMS treatment.
3. To determine the biochemical migraine biomarkers associated with pre and post r-TMS treatment.
4. To determine the clinical neurophysiological parameters among patients with migraine pre and post r-TMS treatment.
5. To examine the neuropsychological findings among patients with migraine pre and post r-TMS treatment.
6. To determine the health-related quality of life (HRQOL) among patients with migraine pre and post r-TMS treatment.
7. To determine the lifestyle factors associated with migraine patients.
8. To identify genetic polymorphism between migraine patients.
8. To evaluate the patient satisfaction measures to TMS treatment.

HYPOTHESIS:

Repetitive Transcranial Magnetic Stimulation as new preventive treatment of episodic migraine.

METHODOLOGY:

This is a single centre, randomised, double-blind, placebo-controlled, parallel group design clinical trial.

NUMBER OF PATIENTS:

The sample size was calculated based on the expected differences in the primary outcome variable, headache days. “Hypothesis testing of two population means” formula was used. With 80% power, 5% level of significance, 30% of attrition calculated sample rate, the sample size for the study was 29 in each arm. Accounting for a drop-out rate of 30%, the sample size will be increased to 38 in each arm. The total sample size will be 76.

NUMBER OF CENTRES: 1

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 more than 50 years
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 as severe hypertension, infections, malignancy, cardiovascular and cerebrovascular diseases, epilepsy degenerative central nervous system diseases, renal failure, hepatic failure, bleeding diathesis and ***serious mental illnesses.***

TEST TREATMENT, DOSE AND MODE OF ADMINISTRATION:

TMS devices treatment, high frequency 20 Hz repetitive stimulation, non-invasive, external application on the scalp

CRITERIA FOR EVALUATION:

Primary Outcome Measure

1. Change from baseline in mean monthly migraine days. The mean monthly migraine days will be calculated using the monthly migraine days from each of the month of the double-blind treatment phase. [Time frame: 4 months after the first session of r-TMS]

Secondary Outcomes Measure

1. Change from baseline in mean monthly migraine attacks. The mean monthly migraine attacks will be calculated using the monthly migraine attack from each of the month of the double-blind treatment phase. [Time frame: 4 months after the first session of r-TMS]
2. Proportion of subjects with at least a 50% reduction from baseline in mean monthly migraine days. [Time Frame: 4 months after first session of r-TMS]. Change from baseline in mean monthly pain intensity of migraine attacks. The mean monthly pain intensity will be based on the record of the maximal pain intensity by means of a verbal scale (i.e. 0 =no headache; 1 = mild headache; 2 = moderate headache; 3 = severe headache) prior to taking symptomatic medication. [Time Frame: 4 months after first session of r-TMS]
3. Frequency and severity of adverse events in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]
4. The DASS 21 score changes in migraine patients in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline for depression, anxiety and stress category.
5. The MIDAS score changes in migraine patients in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline.
6. The MSQ score changes in migraine patients in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline.
7. The EQ-5D score changes in migraine patients in response to r-TMS. [Time Frame: 4 months after the first session of r-TMS. Mean score changes from baseline.
8. The ABNAS score changes in migraine in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline.
9. The PSQI score changes in migraine in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean scores change from baseline.
10. The FFQ score changes in migraine in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline
11. The IPAQ score change in migraine in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline
12. Transcranial Doppler (TCD) pattern changes in migraine patients in response to r-TMS. [Time Frame: Baseline and after treatment sessions (month 4).] Mean flow velocity (cm/s).
13. Electroencephalography (EEG) pattern change in migraine patients in response to r-TMS. [Time Frame: Baseline and after treatment sessions (month 4).] EEG pattern differences based on report.
14. Serum serotonin level and DNA changes in migraine patients in response to r-TMS. [Time Frame: Baseline and after treatment sessions (month 4)] Serum

serotonin (ng/ml).

15. Serum beta-endorphin level changes in migraine patients in response to r-TMS [Time Frame: Baseline and after treatment sessions (month 4)]. Serum beta-endorphin (ng/ml).
16. C-Reactive Protein (CRP) level changes in migraine patients in response to r-TMS [Time Frame: Baseline and after treatment sessions (month 4)] Serum CRP mg/dL
17. Serum Calcitonin gene related peptide (CGRP) level and DNA changes in migraine patients in response to r-TMS. [Time Frame: Baseline and after treatment sessions (month 4)] Serum CGRP pg/mL
18. Satisfaction measures of efficacy, tolerability, safety and expectations of r-TMS among the participants. A 5-point, Likert scale will be used to evaluate satisfaction with r-TMS in migraine prevention. [Time Frame: 4 months after first session of r-TMS]

STATISTICAL METHODS ANALYSIS PLAN

Statistical methods for primary and secondary outcomes

Data analysis will be performed by a medical statistician who is blinded to the entire allocation and treatment process. The SPSS statistical software package vision 22.0 will be used to assess the study data. The intention to-treat principle will be used for all efficacy analyses.

Two-tailed analyses will be performed, with a significant level set at 0.05. Demographic characteristics and baseline measurement of the variables of each group will be summarised. 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, the Kolmogorov-Smirnov test and graphical approach through histogram with a normal curve will be used. Continuous variables will be presented as means ± 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 the between-subject effect (treatment effect), within-subject effect (time effect) and within between-subject effect (treatment time effect) comparisons. Assumptions for the repeated measure ANOVA will be checked, which are assumptions of compound symmetry, normality of residuals and homogeneity of variance. Assumption of compound symmetry will be assessed through Mauchly's test of sphericity, with the normality of residuals 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, a 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 analysed following the same method for primary outcome measure analysis.

Methods for additional analyses (subgroup analyses)

Comparison of the between-subject effects (treatment effect), within-subject effects (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

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