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ASSERT trial – How to assess the safety and efficacy of a high frequency rTMS in postpartum depression? A multicenter, double blinded, randomized, placebo-controlled clinical trial

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Background: Postpartum Depression affects a considerable number of women worldwide. This condition inflicts severe consequences to mother and child health. Thus far, available treatments have low response and high relapse rates. We designed this trial to evaluate a safe and more efficacious innovative therapy.

Aims: To report a feasible and ethical study design to assess the safety and efficacy of a high frequency repetitive Transcranial Magnetic Stimulation 10 Hz (rTMS) compared to sham rTMS in women with moderate to severe Post-Partum Depression using standard treatment (sertraline).

Abstract

BACKGROUND: Postpartum Depression affects a considerable number of women worldwide. This condition inflicts severe consequences to mother and child health. Thus far, available treatments have low response and high relapse rates. We designed this trial to evaluate a safe and more efficacious innovative therapy.

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Keywords:
Postpartum depression
repetitive Transcranial Magnetic Stimulation
Research clinical trial

To conduct an ancillary, exploratory, randomized, active controlled, double blind study with a hypothesis to assess the safety and efficacy of 10 Hz rTMS compared to sertraline.

Methods: A multicenter, parallel arm, randomized, placebo-controlled, double-blind design to assess safety and efficacy of 10 Hz rTMS compared to sham. An ancillary study will be conducted with parallel arm, randomized, active controlled and double dummy design to assess safety and efficacy of 10 Hz rTMS compared to sertraline.

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1. Introduction

As of 2012, the Diagnostic and Statistical Manual of Mental Disorders-5 redefined postpartum depression (PPD) as a subset of Major Depressive Disorder (MDD) persistent up to 4 weeks after delivery with a peripartum onset [1]. Although MDD and PPD share many clinical similarities, a meta-analysis of 11 randomized clinical trials showed differences between the diseases on neuroimaging, gonadal steroid hormonal involvement, and response to treatments [2].

Postpartum Depression has a prevalence of 14% in the general population of pregnant women [3]. It is responsible for maternal suicide and infanticide in the most severe cases [4]. Studies have shown that PPD impairs maternal-newborn bond producing a greater risk of child abuse and negligence; resulting in irreversible cognitive and social deficits later in child life [3,5]. Postpartum depression is the number one cause of maternal morbidity after childbirth [6].

The first-line therapy for moderate to severe PPD is of Selective Serotonin Reuptake Inhibitor (SSRI) such as sertraline [3,7]. Although it is considered relatively safe for breastfeeding, mothers still have a concern regarding newborn consumption of drug metabolites in the breast milk compromising treatment adherence [8,9]. Additionally, the efficacy of SSRI has come into question with low response rates and high relapse rates. High latency to response of these SSRI also plays an important role for this population and reconciling the mother-to-child bond. Hence there is a need to test new therapies for this specific population.

Repetitive Transcranial Magnetic Stimulation (rTMS) is a noninvasive brain stimulation technique that has been FDA approved in the treatment of refractory MDD [10]. rTMS functions by eliciting focal magnetic waves to the brain. It induces neuroplasticity by promoting synaptogenesis in targeted cortical areas [11]. Low frequency rTMS stimulates inhibitory GABA neurons while high frequency stimulates the excitatory neurons. This treatment modality combined with standard therapy has demonstrated a faster response in MDD compared to standard therapy alone [12]. This results in a reduced exposure to SSRI adverse effects.

Only two pilot studies thus far have evaluated the effects of rTMS in PPD patients. Both trials showed safety and positive results of combined therapy of rTMS and SSRI [13,14]. This warrants further investigation of this treatment modality as a viable option in women with PPD to modulate the effect of standard therapy by increasing its efficacy. It has potential to reduce time to response and adverse effect profile of treatment.

In this trial, we aim to investigate the safety and efficacy of high frequency rTMS (10 Hz) compared to sham rTMS in women with moderate to severe PPD using standard therapy (sertraline). This would pave the way towards finding a safe and efficacious evidence-based therapy for postpartum depression and with a better safety profile than standard therapy alone. By adding a third arm, we also aim to conduct an ancillary, exploratory, double dummy study [23] to assess the safety and efficacy of rTMS compared to Sertraline. To our knowledge, this direct comparison has never been evaluated in patients with postpartum depression and would provide a basis for future trials.

2. Methods

2.1. Trial design

A multicenter, parallel arm, randomized, placebo-controlled, double-blind study design to assess safety and efficacy of 10 Hz rTMS compared to sham rTMS in postpartum depressed patients using standard treatment (sertraline). A third arm with patients using 10 Hz rTMS + placebo is needed to address the ancillary hypothesis. The ancillary study will be conducted as a parallel arm, randomized, active controlled and double dummy design to assess safety and efficacy of 10 Hz rTMS compared to sertraline. Subjects will be randomly allocated to either arm 1, 2 or 3 in a 2:2:1 ratio by random blocks of 3 or 6 subjects. Stratification will be done to control for study center.

Treatment will start after delivery once our screening process confirms PPD. Active and sham rTMS will be administered for a 6 weeks Treatment Phase and a 6 weeks Maintenance Phase following pivotal trial and FDA guidelines for TMS and Major Depression [10]. 50 mg Sertraline and placebo will be given for 12 weeks duration with possible increase of an additional 50 mg.

2.2. Participants

Women over 18 years of age, with moderate to severe PPD (based on HAMD-17 scale score >18) will be included. We will exclude patients based on three broad categories of contraindications for rTMS, contraindications for SSRI therapy (for safety), and based on confounders that may affect our outcomes. Table 1 summarizes the eligibility criteria.

2.2.1. Study setting

In order to achieve sufficient generalizability of the results, and to ease the burden of recruitment, this trial will be a multicenter trial. To our knowledge, this is the first multi-center trial testing the safety and efficacy of rTMS in PPD patients. The trial will be conducted at four study sites in USA, Brazil, Portugal and Turkey.

2.2.2. Study site eligibility criteria

1. All necessary equipment and infrastructure available, including qualified, trained and licensed staff, rooms, laboratory with necessary equipment for rTMS.
2. Proven ability to reach recruitment milestones by access to our patients.
3. Approval from the Ethical Committee of each site...
First line treatment of moderate to severe PPD is either Sertraline or Paroxetine. Although both drugs have shown no incidence of infant abnormalities [18], we referred to several systematic reviews and trials comparing SSRI metabolite content in breast milk and in infant abnormalities [18], we referred to several systematic reviews and trials comparing SSRI metabolite content in breast milk and in infant abnormalities. Thus, patients in all arms, will be given the initial dose of 50 mg Sertraline (Arms 1 & 2), or placebo (Arm 3) orally, once daily. The drug will be given at the same time as the rTMS procedure and patients will be given doses to take home during weekend. The dose of sertraline or placebo may be increased by 50 mg per week up to a total of 200 mg, if no improvement within two weeks as deemed by the recommendations of the Data Safety Monitoring Committee.

2.5. Outcome

Our primary endpoint is the absolute change in the 17 item Hamilton Depression Scale Score between patients in Arm 1 and Arm 2. For comparability with previous studies, this validated scale will be our primary outcome to assess efficacy of 10 Hz rTMS over sham rTMS.

Secondary endpoints include adverse event reporting, Edinburgh Post Natal Depression Scale (EPDS) changes, Cortical Silence Period (cSP), 36-item Short Form Survey (SF-36) quality of life scale, and neurocognitive battery tests (Wisconsin card sorting test, controlled oral word association test). Table 3 summarizes the data collection schedule for all the outcomes.

2.6. Randomization

Upon meeting eligibility criteria and signing informed consent, patients will be randomized in a 2:2:1 (Arm 1: Arm 2: Arm 3) ratio in random blocks of 3 or 6 participants per block. Randomization will be stratified by study center. A computer-generated randomization sequence will be issued and an outsider clinician will assign allocation by Interactive Voice Response System.

2.7. Blinding

Investigator, stimulator, assessors, patients, and study staff during the trial will be blinded. Blinded assessors will collect data such as HAM-D17 scale score, SF-36, EPDS, adverse event report. In order to maintain blinding, sertraline will have a matched placebo pill (appearance, texture & taste). Both drugs will be administered in identical containers according to the treatment-code generated by computer randomization. An open label study pharmacist will dispense it.

The trained rTMS operator will be blinded. They will be responsible for applying rTMS treatment and to collect EEG and cSP data after each intervention. To maintain the blinding in this role, we will use the MagVenture TMS device. This device has a two-sided coil; one side is for sham TMS and the other for the active treatment. Both procedures will appear identical. Upon entering the patient ID into the device, it will guide the stimulator to the unmarked appropriate positioning of the coil (sham or active) according to the pre-determined, saved randomization sequence. This feature ensures that the responsible for the brain stimulation remains blinded.

Blinding will be assessed at the end of the trial by a questionnaire completed by stimulators, assessors, investigators and patients. In case of patients dropping out of the study, those will be contacted and encouraged to complete the questionnaire.

2.8. Unblinding

In cases of Severe Adverse Effects (SAE), the Data Safety Monitoring Committee will provide guidance on the need for unblinding. The IVRS system accounts for a code breaking option that only the open label pharmacist has access to. In case of unblinding, investigator will keep records of the date, time, and reasons for unblinding and patient exclusion from the trial. Unblinding is authorized in cases of severe emergency that require information about treatment received by the patient in order to provide appropriate medical care. Unblinding information will only be

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Table 1

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females who have completed delivery</td>
<td>rTMS contraindications</td>
</tr>
<tr>
<td>&gt; 18 years old</td>
<td>Previous Stroke, Seizure or CNS Disease</td>
</tr>
<tr>
<td>Confirmed PPD diagnosis by DSM-5 criteria</td>
<td>Previous or current drug or alcohol abuse</td>
</tr>
<tr>
<td>Moderate to Severe Depression by score of &gt; 18 score on HAM-D17 scale</td>
<td>Ferromagnetic metallic implants</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Treatment phases</th>
<th>Time</th>
<th>Frequency of rTMS administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment phase</td>
<td>Week 1–6</td>
<td>5 times per week</td>
</tr>
<tr>
<td>Maintenance phase</td>
<td>Week 7</td>
<td>3 times per week</td>
</tr>
<tr>
<td></td>
<td>Week 8</td>
<td>2 times per week</td>
</tr>
<tr>
<td></td>
<td>Week 9</td>
<td>1 time per week</td>
</tr>
<tr>
<td></td>
<td>Week 11</td>
<td>1 time per week</td>
</tr>
</tbody>
</table>

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revealed to study staff that is deemed necessary for patient safety.

2.8.1. Discontinuation/stoppage criteria

- Discontinuation from the study may occur under the following circumstances:
  - Patient withdraws consent from the trial.
  - Sudden or severe changes in the patient’s psychiatric, neurological function or general medical condition related to the intervention(s) administered in the trial.
  - Receiving external medical attention that are contraindication to the intervention administered in the trial.
  - Non-compliance.

2.9. Sample size

Sample size was calculated to have 80% power to detect an effect size of 0.67, with a significance alpha level of 0.05 for the primary hypothesis. A drop out rate of 10% was considered. The effect size was estimated based on historical data from previous trials with major depression, SSRI and rTMS [20]. We used this data to base our calculations of the effect size due to the new classification of DSM-V that considers PPD an onset of major depression. All the calculations were performed on Stata providing a final sample size of 100 subjects.

2.10. Statistical analysis

Baseline characteristics will be assessed by ANOVA. The primary outcome will be assessed by t-test. Secondary analysis to control for covariates such as sertraline dose, age, and estrogen level will be performed by ANCOVA with an Intention to Treat (ITT) analysis. Kaplan-Meier and Cox-PH models with censoring for missing data will be used to evaluate time to remission of PPD. For the survival analysis, time-to-remission will be defined as the time to achieve a change of 50% on baseline HAM-D17 scale score through 6 and 12 weeks. Descriptive statistics will be used for safety analysis and EEG changes. Table 4 summarizes the main tests for primary and secondary hypotheses.
Study hypothesis, design, endpoint and statistical analysis.

<table>
<thead>
<tr>
<th>Treatment ARM1</th>
<th>Treatment ARM 2</th>
<th>Endpoints</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hypothesis</td>
<td>- 6-week Treatment phase: 10 Hz rTMS +50 mg Sertraline once daily</td>
<td>- 6-week Treatment phase: Sham rTMS protocol +50 mg Sertraline</td>
<td>Primary: Reduction of 50% baseline HAM-D17 scale score</td>
</tr>
<tr>
<td>- 6-week Maintenance phase: 10 Hz rTMS + Sertraline</td>
<td>- 6-week Maintenance phase: Sham rTMS protocol + 50 mg Sertraline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment ARM 2</td>
<td>Treatment ARM 3</td>
<td>Endpoints</td>
<td>Statistical analysis</td>
</tr>
<tr>
<td>Secondary hypothesis</td>
<td>- 6-week Treatment phase: Sham rTMS protocol +50 mg Setraline</td>
<td>- 6-week treatment phase: 10 Hz rTMS protocol + Placebo</td>
<td>Unpaired t-test based on Central Limit Theorem</td>
</tr>
<tr>
<td>- 6-week Maintenance phase: Sham rTMS protocol +50 mg Sertraline</td>
<td>- 6-week maintenance phase: 10 Hz rTMS + placebo</td>
<td>Secondary: Reduction of 50% baseline HAM-D17 scale score after 6 weeks and 12 weeks time points</td>
<td></td>
</tr>
</tbody>
</table>
3.3. Ethical considerations

In dealing with a vulnerable population such as pregnant women with a moderate to severe psychiatric condition, sound ethical rationale must be incorporated into our study design. Firstly, safety of rTMS procedure has been repeatedly demonstrated in the general population and specifically in PPD patients in pilot studies [13,14]. Secondly, since the effects of rTMS on pregnant women have not been established to date, we will only initiate treatment post-delivery. Thirdly, our randomization ratio allows for 80% of patients to receive standard therapy with active or sham rTMS treatment. Only 20% of our patients will receive rTMS alone. Although rTMS monotherapy has a proven efficacy in MDD [22], we will employ a Data Safety Monitoring Committee to oversee all the trial data in a blinded fashion on an ongoing basis. Patients with worsening symptoms, or serious adverse events, will be evaluated by the DSMC and guidance will be given in regards to SSRI dose adjustment, unblinding, reverting to standard therapy or discontinuation.

3.4. Limitations

In designing this trial, we perceive limitations that need to be addressed. Blinding in medical device trials is a well-known challenge. In addition, our ancillary study may simply serve as a pilot arm and results should be interpreted as such. The MagVenture TMS device provides the added feature of an unmarked single, two-sided coil for both sham and active treatments allowing for a blinded operator. However, there are inevitable telltale signs of active and sham treatments by an experienced stimulator. For instance, muscle twitches intensity during calibration by motor threshold and the stimulation itself. For this reason, we will add an additional layer of protection against unblinding by ensuring our blinded stimulator is unrelated to any other trial activities, data analysis, and have limited contact with researchers. By the same mechanism, patients with previous experience with active rTMS may be unblinded by the differences between sham and active treatments sensation. Therefore, these patients will be excluded from the trial.

3.5. Strengths

We find that this trial design allows for an ethical alternative to evaluate a particularly vulnerable population that is difficult to study. This trial has the benefit of evaluating rTMS as a combination therapy as well as an exploratory monotherapy as a basis for future trials. The ancillary exploration fills a gap in the literature that has not been previously explored in this population. Furthermore, our robust design, tests two parallel hypotheses using easily interpretable statistical tests. Because of the strong evidence of TMS in depressive disorders and FDA approval for this indication, we have strongly validated outcomes to evaluate its efficacy and a well-established rationale for our hypothesis, making it likely to show positive results.

4. Conclusion

We designed a study protocol scientifically feasible, ethical for the investigation of an innovative treatment for PPD. In addition, this subject is relevant for the scientific community, and has an impact on women’s health care and on public health.

Acknowledgements

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References

[6] Cindy-Lee Dennis, Peer support for postpartum depression: volunteers’ perceptions, recruitment strategies and training from a randomized controlled trial, Health Promote Int. 28 (2) (June 2013) 187–196.