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An Open Label Feasibility Study on Impact of rTMS Versus Drug Therapy on Phantom Limb Pain in Lower Limb Amputation Patients: A Randomized Controlled Trial

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Abstract

Background: Phantom limb phenomena, a sensation in a lost body part, have been a medical and folklore issue since 1797. In amputees, phantom limb pain (PLP) is common, with incidence ranging from 42.2 to 78.8%. Multidisciplinary treatment required for management of PLP.

Objective: The purpose of the current study is to compare the efficacy of repetitive transcranial magnetic stimulation (rTMS) comparted to drug therapy in the management of phantom limb pain (PLP), as well as to assess rTMS effectiveness at the fourth- and eighth-weeks following amputation.

Methods: A prospective randomized controlled trial with ethical approval and trial registry is planned with a pilot sample size of 50 patients. The study includes patients aged 18-65, all genders, undergoing traumatic lower limb amputation, reporting phantom limb pain, without ICU stay exceeding 48 hours. Patients in rTMS group will undergo 10 continuous sessions, lasting 15 minutes each. 30 trains of magnetic pulses, each lasting 20 seconds, will be applied at 1Hz over left motor cortex, at 80% of the resting motor threshold, with a 10-second inter-train interval. Patients in drug therapy group will receive monitored drug dispensing, including a combination of medications as per the Institute's protocol. Patients will be assessed for psychological scales and serotonin 5 HT at fourth- and eighth-week post amputation.

Results: It is expected that rTMS therapy which is non-invasive will reduce the usage of drug therapy in management of phantom limb pain.

Conclusion: The study will investigate the safety and feasibility of using rTMS in traumatic lower limb amputation patients for managing phantom limb pain, comparing it with drug therapy.

Keywords: rTMS; Phantom Limb Pain; Lower Limb Amputation; Limb Loss; Traumatic Amputation; Trauma

Abbreviations

PLP: Phantom Limb Pain; rTMS: Repetitive Transcranial Magnetic Stimulation; RMT: Resting Motor Threshold; LMC: Left Motor Cortex; MEP: Motor Evoked Potential; NRS: Numerical Rating Scale; MPQ: McGill Pain Questionnaire; HADS: Hospital Anxiety and Depression Scale; CGIS: TMS: Transcranial Magnetic Stimulation.

Introduction

People all over the world who have had limbs amputated have impaired physical ability and mobility which is reported to have regional differences. In high-income countries, peripheral vascular disease and diabetes are frequently cited as the main cause of limb amputations however, in several low- and middle-income countries trauma is the main cause of limb amputation [1,2]. Traumatic leg amputation affects young, active individuals, causing long-term consequences and impacting their health-related quality of life [3]. Phantom limb phenomena, which refer to sensations in a lost body part, have been a well-known phenomenon in medicine and folklore for a long time since 1797 [4]. The majority of amputees report feeling the missing limb in some way, and the majority also have phantom limb pain (PLP) [5-7]. There have been reports that the incidence of PLP in patients who require amputation ranges from 42.2 to 78.8% [8-9]. Management of phantom limb pain, often require multidisciplinary approaches for effective treatment, with current studies focusing on repetitive Transcranial Magnetic Stimulation (rTMS) [10]. Present study aims to investigate the impact of repetitive Transcranial Magnetic Stimulation (rTMS) on Phantom Limb Pain (PLP) management, also compares rTMS with Drug Therapy, and evaluates its effectiveness at fourth- and eighth-weeks post-amputation.

Methodology

Ethical Consideration and Trial Registration: The study is approved from the Institute Ethics Committee (Ref. No. IEC-33/07.02.2020, RP-06/2020) and Clinical Trials Registry-India: REF/2020/06/034643.

Design: The study is Prospective Randomized Controlled Trial

Sample size, patient population and randomization: This is a pilot study and a convenient sample size of 50 is taken. Patients will be recruited from the IPD pool received in the Emergency Department of level- I trauma centre. Study participants will be randomized into either group A (rTMS therapy) or group B (drug therapy), which will be done through a computer-generated random sequence of numbers in a block of 4. This sequence of numbers will be kept in a sealed envelope in the office of PI. The envelopes will be opened by the person who will not be directly involved in the trial.

Inclusion and exclusion criteria: Patients received in In- patient department who are hemodynamically stable undergoing traumatic lower limb amputation, between the age of 18-65, all gender and not necessitating ICU stay for more than 48 hours and reporting phantom limb pain at least once in a day will be included in the study. The exclusion criteria of the study will be revision amputation patients, pregnant women, co-morbidities like cardiac condition, malignancies, coagulation and bleeding disorders, patients on anti-epileptics and thyroid drugs, patient not giving consent and patients with known psychiatric illness.

rTMS Protocol

rTMS therapy will be given to patients of group A (intervention group) for 10 continuous sessions post amputation as early as patient is hemodynamically stable and feasible to shift the patient to pain lab. The duration of each rTMS session will be 15 minutes. During treatment, 30 trains of magnetic pulses will be given. Each train lasts for 20 seconds. The frequency of these trains is 1Hz at 80% of the Resting Motor Threshold (RMT) with a 10 second inter-train interval (a total of 600 stimuli per session) will be applied over the left motor cortex.

rTMS Therapy Administration

Before the beginning of the first rTMS session, the Resting Motor Threshold (RMT) of the patient will be determined. This is done by determining the motor hotspot, the distance from the left pre-ocular region to the right pre-ocular region is measured. Thereafter, the distance between the nasion to the inion is measured. The intersection between these two points is marked; which is known as the Cz point. From the Cz point, a distance of 5 cm is measured laterally towards the left. From this point, 2 cm is measured in the anterior direction. This spot is the motor hotspot. The electrodes of the EMG machine will be placed on the motor hotspot. RMT will be determined using single-pulse stimulation over the Left Motor Cortex (LMC). Motor Evoked Potential (MEP) will be recorded at the abductor pollicis brevis muscle in the right hand and on the EMG monitor. Discrepancy in MEP (twitch is observed in the right-hand muscle but not on the EMG monitor, and vice-versa) can be attributed to manufacture defect or incorrectly placed electrodes. RMT is defined as the lowest intensity required to elicit a motor evoked potential of 50 μV in 50% of successive trials. Once RMT is obtained, first rTMS session will be started. The machine is plugged into a socket and can be switched on or off from a single switch, as per requirement. The machine consists of a monitor and keyboard; this is used to enter the patient details (name, age, date of birth) and the settings for their rTMS sessions. After entering patient details and the settings of the rTMS sessions, the patient will be given rTMS therapy. The patient will be seated in a reclined position. The chair on which the patient is seated is covered in foam. This is because the chair

should not have any metal in contact with the patient's body which is a contraindication for rTMS therapy. During rTMS sessions, figure of eight electromagnetic coil will be placed on the Left Motor Cortex. rTMS sessions will be delivered at 80% of the RMT at 1 Hz as mentioned in our study protocol. The duration of the session is 15 minutes. During the session, 30 trains of magnetic pulses are delivered; each train lasts for 20 seconds with a 10 second inter-train interval. rTMS therapy is given over 10 sessions (1 session per day) over the period of 2 weeks.

Drug Therapy Protocol

Drug therapy will be given to patients of group B were, monitored drug dispensing will be done for the control group as per Institute's protocol. This includes a combination of Acetaminophen, NSAIDS, Opioids, Antidepressants, Anticonvulsants, Beta blockers, Muscles Relaxants, TCA, Lidocaine, NMDA, antagonists, Clonidine etc.
Currently followed drug regime for management of phantom limb pain as per Institute's protocol

- NSAIDS (Nonsteroidal anti-inflammatory drugs)
  Paracetamol (500 mg)
  Escalated to

↓

Gabapentin (Anti -Convulsant)
(300 mg-2400 mg/Day) in titrating dose

IF NO RESPONSE, SWITCH TO
- Amitriptyline (TCA) (55mg/Day)

↓

- SNRI (Serotonin Norepinephrine reuptake inhibitors)

1. Another Anti-depressant class is kept in reserve and advise by psychiatrist on consultation (Duloxetine / Venlafaxine).

If Drug Therapy Fails

1. Pain team along with Department of Anesthesia and Critical care of the hospital will be contacted if conventional drug treatment requires escalation for opioids or neuromuscular blockade.

2. Since pain is patient specific and very subjective, the patients who will not respond to the drug management as per above protocol and required the need for neuromuscular blockade, will be excluded from the study. This will be done in order to maintain uniformity among patients of the control group, so patients are neither over-medicated nor under medicated.

Outcome Measures

- **Serotonin (5-hydroxy tryptamine, 5-HT):** Serotonin in the brain regulates anxiety, happiness, and mood. Low levels of the chemical have been associated with depression, and increased serotonin levels brought on by medication are thought to decrease arousal. Nearly all known antidepressants and anti-anxiety drugs affect 5-HT transmission. This will be assessed within 24 hours after amputation through blood sample. Second assessment is done at 8-weeks post-amputation.
- **Pain Rating Scale:** The Numerical Rating Scale (NRS) is a psychometric scale that yields a pain score between 0 to 10. It is a unidirectional and continuous scale where 0 indicates 'no pain' and 10 indicates 'maximum tolerable pain'. It is a self-report measure. This is used to assess severity of phantom limb pain. Baseline assessment is done within 48 hours after amputation. Second assessment is done at 4 weeks and third assessment at 8 weeks of amputation.
- **McGill Pain Questionnaire (MPQ):** The McGill Pain Questionnaire (MPQ) is composed of 78 descriptive items which respondents choose to describe their experience of pain. The 78 items are further categorized into 20 subclasses. Further categories are as follows; Sensory (questions 1-10), Affective (questions 11-15), Evaluative (question 16), and Miscellaneous (question 17-20). This is used to assess phantom limb pain. Baseline assessment is done within 48 hours after amputation. Second assessment is done at 4 weeks and third assessment at 8 weeks of amputation.
- **The Hospital Anxiety and Depression scale (HADS):** The Hospital Anxiety and Depression scale (HADS) is a valid and reliable self-rating scale that measures both anxiety and depression in a general medical population of patients. This is used to assess anxiety and depression levels in patients. Baseline assessment is done within 48 hours after amputation. Second assessment is done at 4 weeks and third assessment at 8 weeks of amputation.
- **Clinical Global Impression Scale:** The CGI scale requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have had the same diagnosis. It is a 3-item, observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response. The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). CGI-C scores range from 1 (very much improved) through to 7 (very much worse). Baseline assessment is done within 48 hours of amputation. Second assessment is done at 4 weeks and third assessment at 8 weeks of amputation.
- **Procedure:** Patients with traumatic lower limb

amputation, will be screened for inclusion and exclusion criteria. After satisfying the relevant criteria, they will be briefed about the study and thereafter informed consent will be obtained. A study ID (R-n) will be assigned to all the patients. Thereafter, patient will be randomized into two groups; group A (intervention group) and group B (control group). Patient's blood sample will be drawn within 24 hours after amputation to measure for the blood marker of serotonin (5 hydroxy tryptamine, 5 HT). 3 vials of blood are collected; 2 SST tube (yellow vial) and 1 EDTA tube (purple vial). Blood samples will be processed and stored in the Department of Laboratory Medicine at -80 degree Celsius under the supervision of the co-investigator from the Department of Lab Medicine. Second collection of the blood marker will be done at 8 weeks after amputation. After this, assessment will be done by psychologist for the outcome measures using psychological scales which will include Pain rating scale, McGill pain questionnaire, Hospital anxiety and depression scale and Clinical global impression. This will be done within 48 hours after amputation. Follow up assessment for the same, will be done at 4 weeks and 8 weeks post amputation. If the patient requires ICU stay post-surgery, then assessment by psychologist will be done once the patient is out of the ICU. However, if ICU stay is more than 48 hours then patient will be excluded from the study as post randomization exclusion. A consent sheet apart from PIS and PICF will be developed in consensus with investigators regarding precautions and safety related to administration of rTMS therapy. Patients who will be randomized to group A will receive rTMS therapy once patient is hemodynamically stable and feasible to shift to pain lab as early as possible after baseline assessment is complete. Patients randomized to group B will receive drug therapy as per the institute's protocol. For follow up, patients will be called in Amputation Clinic which is a dedicated clinic for amputation patients at our centre on every Monday at 2pm for regular follow-up regarding stump care, pain management, physiotherapy, stump preparation for prosthesis, peer mentoring and counselling regarding prosthesis application. Apart from this patient will be called telephonically on weekly basis, for regular follow-up.

Data Collection and Statistical Analysis

An MS Excel spreadsheet program will be used to record and code the data. For continuous variables, mean/standard deviations and medians/IQRs will be used; for categorical variables, frequencies and percentages will be used in the descriptive analysis. The Mann-Whitney U-test will be used to compare the non-normal variables, and the student's t-test will be used to compare the normal variables. Analysis for primary outcomes will be conducted with an intention to treat. At p value <0.05, statistical significance will be maintained.

Results

It is expected that rTMS therapy which is non-invasive will reduce the usage of drug therapy in management of phantom limb pain. Adequate management of phantom limb pain will improve quality of life of an amputee patient (Figure 1).

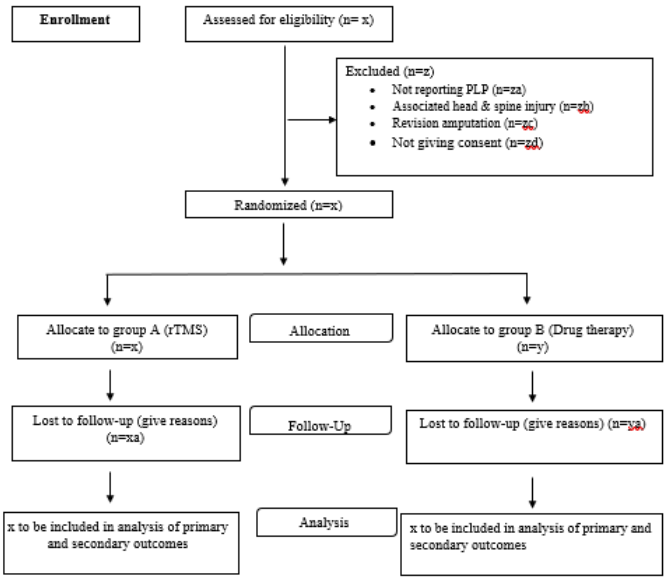

Figure 1: Flow Chart.

Discussion

PLP either following trauma or non-trauma amputations is a condition that is often overlooked in the context of post-amputation recovery. Despite being identified since 1551, PLP is complicated, and its pathophysiology is still not fully understood. PLP has been explained by multiple theories, but the most common is the "theory of mal-adaptive plasticity," which holds that it is not just confined to the sensorimotor cortex but also involves cortical reconfiguration following amputation [11]. It also affects one's overall quality of life and has been associated to higher rates of depression and anxiety [12]. However, there is currently no satisfactory treatment for persistent phantom limb pain.10 An electromagnetic coil is used in transcranial magnetic stimulation (TMS), which is a non-invasive, safe technique, to create a magnetic field by generating brief magnetic pulses that readily and painlessly travel through the skull and into the brain. TMS can stimulate the cortex of the brain both at the stimulation site and transapically in other areas, these pulses cause alterations in cortical excitability [13,14]. The possibility of rTMS to stop maladaptive sensorimotor cortical remapping has been investigated in other conditions but not in management of phantom limb pain following trauma, since our study is addressing traumatic amputee population. The results will be useful for managing PLP following non traumatic amputation as well. Studies have demonstrated a substantial reduction in PLP from baseline values after rTMS intervention [15,16].

It is challenging to choose the first-line therapy for PLP, such as non-pharmacologic vs. pharmacologic alternatives, due to the absence of clinical recommendations.10 Present study is a randomized controlled trial which will aid in demonstrating the direct cause-and-effect link between an intervention and the result of treatment. This will enable the most efficient evaluation of rTMS impact in management of phantom limb pain along with comparing the effect with drug therapy and minimizing its use. The findings can aid in the prioritization and improvement in management and treatment strategies for phantom limb pain for medical professionals and healthcare providers. Also, the findings of our research will provide substantial evidence for using low frequency rTMS in managing in phantom limb pain irrespective of cause of amputation, either traumatic or non-traumatic.

Conclusion

Present study will examine the feasibility and safety of administrating rTMS in traumatic lower limb amputation patients for management of phantom limb pain. Along with this, the study will also compare its effect with drug therapy and if rTMS has a role in minimizing the usage of drug therapy. The study will also discuss the limitations of using rTMS in a resource limited settings along with potential confounders when the study will conclude.

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