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Role of TMS in Improving the Nerve Functions in Radial, Median, and Ulnar Neuritis Among Patients with Leprosy: Study Protocol for a Randomized Controlled Trial

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Abstract

Objectives: The overall aim of this RCT is to evaluate the role of Trans-cranial Magnetic Stimulation (TMS) as a new treatment approach in physiotherapy-based rehabilitation in leprosy patients. More specifically, the primary objective of this study is to study the effect of TMS in leprosy patients with median, radial, and/or ulnar neuritis from <6 months. The secondary objective is to establish TMS as a therapeutic tool to treat leprosy patients effectively. **Methods: Study Population -** 98 diagnosed leprosy patients with ulnar, median, and or radial nerve function impartment for <6 months duration attending the out-patient department in CSSH Subharti Hospital, Meerut. We will include clinically diagnosed leprosy patients with median, radial, and/or ulnar neuritis from <6 months. **Intervention -** For Group A, TMS mapping of four hand target muscles will be performed In this group, each participant will receive ten treatment sessions of 30 min with high frequency 5-Hz TMS for 2 weeks. Along with TMS, home exercise program including standard exercises will be given. For group B, only home exercise program including standard will be given. **Outcome Measures -** To measure the outcomes of the study, the tools used will be electromyography, nerve conduction velocity, brain derived neurotrophic factor, manual muscle testing, monofilament sensory testing, and hand dynamometry. **Statistical Analysis -** F test and repeated-measures ANOVA between the factors will be used for the testing of this randomized control trial study. **Discussion:** It was believed that the leprosy only affects the peripheral nerves without affecting the brain but recent studies showed that brain plasticity can also occur following amputation, nerve damage, or injury. It is proved in various studies stated that the damage caused by leprosy is not limited to peripheral nerve only and is the evidence for brain plasticity. It is stated in many studies that, TMS can also be used as a neuro-modulatory tool and the application of TMS leads to improved motor performance and it also induces evident changes in connectivity in the interconnected regions of the brain but no literature evidence is available on the role of TMS in leprosy. **Conclusion:** In our study, we will try to fill this knowledge gap on the role of TMS as a therapeutic tool in patients with leprosy.

Keywords: Brain-derived neurotrophic factor, Electromyography and nerve conduction velocity, Randomized controlled trial, Trans-cranial magnetic stimulation

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Introduction

Leprosy or Hansen's disease is a chronic infectious disease affecting skin and nerves.[1] According to official figures from 145 countries, 216 108 new leprosy cases were registered globally in the year 2016. The prevalence rate corresponds to 0.29/10,000 on the basis of 173 358 cases at the end of the year 2016.[2]

In the year 2015–16, 0.88 lakh leprosy cases were recorded, with a prevalence rate of 0.69/10,000. During 2015–16 detailed information on new cases indicates the proportion of MB (51.27%), child (8.94%), female (38.33%), ST cases (18.79%), SC cases (18.57%), and Grade II deformity (4.60%). During 2015–16, a total of 5851 with Grade II disability detected among the new cases of leprosy, indicating the Grade II disability rate of 4.46/million population.[3]

Although the leprosy is curable by multi-drug therapy but irreversible changes in the peripheral nerves results in mild, moderate, or severe deformities depending on the number and extent of involvement of the peripheral nerves leading to physical disability.[4]

Earlier it was believed that no major changes in the brain occur after childhood. However, recent studies showed that brain plasticity can also occur following amputation, nerve damage, or injury. It was believed that the leprosy only affects the peripheral nerves without affecting the brain but a study done by a multi-disciplinary team of researchers at the Federal University of Rio de Janeiro concluded that the damage to the peripheral nerves caused by leprosy can lead to neuroplastic changes in the brain. In this study, trans-cranial magnetic stimulation (TMS) was used to establish the connection between the brain and the hand grip muscles in adult leprosy patients with claw hand deformity and concluded that the representation for a given muscle in the brain may change and thus the damage caused by leprosy is not limited to peripheral nerve only and is the evidence for brain plasticity.[5]

In a study by Liew *et al*., the non-invasive brain stimulation has been studied as an adjuvant in neuro-rehabilitative treatment. The research focused on two most commonly used non-invasive brain stimulation techniques - trans-cranial direct current stimulation

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and TMS and discussed the evidence for their application in neuro-rehabilitation. The study established that TMS can be used for assessing neuro-physiological processes and it also influences the function of the brain.[6] A study by Sandrini and Cohen, discusses the use of NIBS in neuro-rehabilitation. It mentions that the NIBS after repeated stimulation have long-term effects on cortical excitability and depending on parameters of stimulation excitability of motor cortex can be reduced or enhanced.[7]

The overall aim of this RCT is to evaluate the role of TMS as a new treatment approach in physiotherapy based rehabilitation in leprosy patients. However, to the best of our knowledge, none of the studies has focused toward the role of TMS in leprosy; therefore, the above stated reasons highlight the need of a new approach to treat the leprosy patients.

Materials and Methods

Study Population

Diagnosed leprosy patients with ulnar, median, and or radial nerve function impartment for <6 months duration attending the outpatient department in CSSH Subharti Hospital, Meerut. We will include clinically diagnosed leprosy patients with median, radial, and/or ulnar neuritis from <6 months. Patients with history of upper extremity fracture, history of neurological deficits, stroke, demyelinating disorders, diabetes, migraine, headache, systemic disease, on medications affecting central nervous system, and cardiac pacemaker placement will be excluded from the study.

Intervention

98 clinically diagnosed leprosy patients with median, radial, and/or ulnar neuritis from <6 months will be included after filling leprosy patient card/record, informed consent form, and information sheet.

For Group A-Steroid Therapy

Patients in 1st week of steroids treatment will only be included (according to the WHO guidelines). TMS - TMS mapping of four hand target muscles (Flexor Digitorum Superficialis, Abductor Pollicis Brevis, First Dorsal Interossei and Abductor DigitiMinimi) will be performed. In this group, each participant will receive ten treatment sessions of 30 min with high frequency 5-Hz TMS for 2 weeks (5 sessions/week). Along with TMS, Electromyography (EMG) recordings will also be obtained by measuring latency and peak-to-peak MEP amplitudes. The MEPs mean amplitude recorded at each stimulated point will be subsequently calculated and projected onto the brain to create a cortical-muscle representation map. EMG readings will be visually checked to ensure that all muscles are electrically silent during the procedure. Home exercise program - Standard exercises: Active range of motion exercises for wrist, metacarpo-phalangeal, proximal inter-phalangeal and distal inter-phalangeal joints, massage of hands includes - kneeding, circular friction massage and stroking and grip strengthening exercises with "sqeezy" ball.

For Group B-Steroid Therapy

Patients in 1st week of steroids treatment will only be included (according to the WHO guidelines). Home exercise program - Standard exercises: Active range of motion exercises for wrist, metacarpo-phalangeal, proximal inter-phalangeal and distal inter-phalangeal joints, massage of hands includes - kneeding, circular friction massage and stroking and grip strengthening exercises with "sqeezy" ball.

Results

EMG and nerve conduction velocity (NCV) testing will be used to study the motor conduction of radial, median, and ulnar nerves. The motor action potentials amplitude and motor conduction velocities will be measured. To study sensory conduction in the same nerves the sensory action potential amplitude and sensory conduction velocity will be measured.[8] NCV recordings will be recorded on 1st day before starting the sessions and on 1st and 21st days of the sessions. Brain-derived neurotrophic factor (BDNF) (a bio-marker for neuroplasticity) has an important role in determining neuroplasticity. Level of BDNF in blood plays an important role in determining neuroplasticity.[9] BDNF readings will be recorded on 1st day before starting the sessions and on 21st day after completing the sessions. Manual muscle testing (MMT) to assess impairments and deficits in muscle performance, including strength, power, or endurance. MMT readings will be recorded on 1st and 10th day of the sessions. Monofilament sensory testing will be used in assessing the impairment in the sensory functions of the nerve. Sensory testing readings will be recorded on 1st and 10th day of the sessions. Hand dynamometry is a simple, non-invasive method to assess the strength of the muscles of upper extremities. Hand dynamometry readings will be recorded on 1st and 10th day of the sessions.

Dissemination of the Results

In the preparation of the manuscripts reporting the result of this RCT, the Consolidated Standards of Reporting trials guidelines will be used. The results of this RCT will be published in National/International peer-reviewed journals.[10] A summary of the results of the study will also be posted at ctri.nic.in. Authors of the publications will contribute in the preparation of the manuscript, elaboration of the protocol, implementation, and conduct of the trial and writing the report. Data will only be shared to the participants and access to full protocol can be granted to anyone on request.

Statistical Analysis

F test and repeated-measures ANOVA between the factors will be used for the testing of this randomized control trial study.

Discussion

It was believed that the leprosy only affects the peripheral nerves without affecting the brain but recent studies showed that brain plasticity can also occur following amputation, nerve damage, or injury. A study done by a multi-disciplinary team of researchers at the Federal University of Rio de Janeiro concluded that the damage to the peripheral nerves caused by leprosy can lead to changes in the brain. In this study, TMS was used to establish the connection between the brain and the hand grip muscles in adult leprosy patients with claw hand deformity. The study concluded that the representation for a given muscle in the brain may change and thus the damage caused by leprosy is not limited to peripheral nerve only and is the evidence for brain plasticity.[6] A variety of causes exists which can lead to the rise in peripheral neuropathies, the current treatment approaches for peripheral neuropathies are based on the elimination of the triggering cause but it is still a challenging task to bring improvement in nerve fiber reparation. This gives boost to translating the concept of neuroplasticity into clinical therapies.[11] Brain-derived neurotrophin factor is identified as the key mediator in motor learning. It's secretion through activity-dependent pathway plays a major role in promoting neural plasticity in the areas activated in response to experience.[12] A study by Fernando Gomez-Pinilla investigated the potential mechanisms through which exercises can be used to lead to neuroplastic changes in the brain. The results showed that the expression for BDNF and its receptor was increased by exercises. This study also concluded that to maintain the potential for neuroplasticity and normal BDNF levels in the neuro-muscular system, basal levels of motor activity are required.[13] Kluding conducted a study on effect of aerobic exercises and strengthening exercises on subjects with diabetic peripheral neuropathy and concluded that supervised exercises shows evident improvements in neuropathic and cutaneous nerve fiber branching in diabetic peripheral neuropathy.[14] A review by Hosp *et al*. on cortical plasticity during motor learning in stroke patients focused on the new movement sequences in healthy individuals, spontaneous cortical re-organization and the coincidences skilled motor re-learning and spontaneous re-organization with a exercised based training for neuro-rehabilitation. It concluded that relationship exists between the motor learning and motor cortex plasticity.[15] A study conducted by Rossini and Dal Forno suggested that TMS, PET, EEG, fMRI, and MEG are useful in studying representation of the hand in the brain and inter-hemispheric asymmetries in normal and pathological conditions. The study also stated that MEG and TMS allows early detection of sensory and motor changes in the brain.[16] Non-invasive brain stimulation uses electrical or magnetically induced currents application through the scalp to stimulate areas of the brain and can temporarily excite or inhibit the activity of the brain in the target regions. A study by Liew *et al*. established that TMS influences brain function and can be used to assess neuro-physiological processes. This study also stated that, TMS can also be used as a neuro-modulatory tool. Altogether these studies suggested that the application of TMS leads to improved motor performance and it also induces substantial connectivity changes in interconnected brain regions.[7]

It is proved in various studies stated above that the damage caused by leprosy is not limited to peripheral nerve only and is the evidence for brain plasticity. It is stated in many studies that, TMS can also be used as a neuro-modulatory tool and the application of TMS leads to improved motor performance and it also induces evident changes in connectivity in the interconnected regions of the brain but no literature evidence is available on the role of TMS in leprosy.

Conclusion

This RCT will provide a solution to the problems related to physical impairment in the leprosy patients and provide a new approach to the physiotherapy based rehabilitation by providing knowledge of neuroplastic changes in new cases of leprosy having signs of nerve involvement but no visible deformity. It is important to focus on preventing the physical disabilities by maintaining the motor functions otherwise; it will lead to more pronounced functional impairments.

Ethics Approval and Consent to Participate

Ethics approval has been confirmed from the Institutional Ethical Committee of Lovely Professional University, Punjab (LPU/IEC/2019/02/03). The inclusion of a patient will be finalized after obtaining their signature on the patient information sheets and consent forms.

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