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Cortical intermittent theta burst stimulation on gait pathomechanics and urinary tract dysfunction in incomplete spinal cord injury patients: Protocol for a randomized controlled trial

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ARTICLE INFO

Method name:
This is a Protocol Article of a Randomized Controlled Trial

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ABSTRACT

Gait impairment and neurogenic bladder are co-existing common findings in incomplete spinal cord injury (iSCI). Repetitive transcranial magnetic stimulation (rTMS), evident to be a promising strategy adjunct to physical rehabilitation to regain normal ambulation in SCI. However, there is a need to evaluate the role of Intermittent theta burst stimulation (iTBS), a type of patterned rTMS in restoring gait and neurogenic bladder in SCI patients. The aim of the present study is to quantify the effect of iTBS on spatiotemporal, kinetic, and kinematic parameters of gait and neurogenic bladder dyssynergia in iSCI. After maturing all exclusion and inclusion criteria, thirty iSCI patients will be randomly divided into three groups: Group-A (sham), Group-B (active rTMS) and Group-C (active iTBS). Each group will receive stimulation adjunct to physical rehabilitation for 2 weeks. All patients will undergo gait analysis, as well assessment of bladder, electrophysiological, neurological, functional, and psychosocial parameters. All parameters will be assessed at baseline and 6th week (1st follow-up). Parameters except urodynamics and gait analysis will also be assessed after the end of the 2 weeks of the intervention (post-intervention) and at 12th week (2nd follow-up). Appropriate statistical analysis will be done using various parametric and non-parametric tests based on results.

Specifications table

Subject area:	Medicine and Dentistry.
More specific subject area:	Spinal Cord Injury.
Name of your protocol:	Cortical Intermittent theta burst stimulation on gait pathomechanics and urinary tract dysfunction in incomplete spinal cord injury patients: Protocol for a randomized controlled trial.
Reagents/tools:	Transcranial magnetic stimulation (Neurosoft MS/D).
Experimental design:	A double-blind (investigator and patient), prospective, randomized, placebo-controlled study.
Trial registration:	Trial is being registered with the Clinical Trial Registry-India (CTRI) number- CTRI/2023/08/056,150.

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Ethics:	Ethical approval has been obtained from Institute Ethics Committee, AIIMS, New Delhi (IECPG-312/07.06.2023, RT-10/20.07.2023). Informed, voluntary, and written consent will be taken from all participants before recruitment into the study. Participants will be given a choice to withdraw from the study at any given point in time.
Value of the Protocol:	• This study will evaluate and assess two most crucial symptoms of spinal cord injury (gait impairment and neurogenic lower urinary tract dysfunction) that makes the patients socio-economically compromised, bedridden and even potential cause of death. • Successful completion of this trial potentially retrieves the functional independence and establishes bladder synergia. • This project will address the global spinal injury community to enhance the quality of life. Simultaneously benefit care giver, rehabilitation experts, clinicians, and researchers.

Description of protocol

Introduction

Spinal cord injury (SCI) impairs sensory, motor, and autonomic functions resulting from traumatic and non-traumatic events [1,2]. Profound functional disability and severe socio-economic crisis make SCI a top neurological burden disease affecting the global population [3]. Depending upon the level and extent of cord damage, prognostic outcomes can be predicted [4]. Loss of voluntary functions and bladder (detrusor) dyssynergia are two crucial symptoms of SCI having immense clinical significance, hence to be managed with great care [5,6]. Extensive reorganizations of remaining neural circuits at cortical, subcortical levels and guided plasticity may contribute to optimizing functional recovery [7]. Even in modulating bladder control synaptic plasticity plays an important role [8]. In the present decade, repetitive transcranial magnetic stimulation (rTMS) has become a reliable modality for treating SCI and other neurological diseases [9]. This advance, non-invasive, diagnostic, and therapeutic tool changes cortical excitability, induces long-term potentiation or long-term depression and promotes neural repair, regeneration, and plasticity [10]. Intermittent theta burst stimulation (iTBS) is a specific stimulation mode of rTMS. Previous studies have shown high frequency, low-intensity application of iTBS produces a long sustained excitable cortico-spinal neuronal drive that reflects a predominant therapeutic effect compared to the traditional effect of rTMS [11].

Physical rehabilitation is often recommended adjunct to transcranial magnetic stimulation (TMS) to achieve optimum recovery. The key concept of physical rehabilitation is based on activity-dependent plasticity and motor re-learning [12]. Patients with incomplete spinal cord injury (iSCI) have the potential to regain ambulation in terms of walking speed, stride length, step length, and cadence after applying iTBS along with physical rehabilitation [13]. Different deformities are present at hip, knee, and ankle joints in iSCI patients that hinder achieving normal gait function as well as the quality gets compromised [14]. To analyse such gait pathomechanics, a detailed kinematic and kinetic parameters assessment and the effect of iTBS on those parameters in the gait function needs to be done. Similarly, neurogenic lower urinary tract dysfunction is one of the most common symptoms but unfortunately, no studies have been done to assess bladder function following iTBS administration.

Our study aims to quantify the effect of iTBS on gait pathomechanics and neurogenic bladder dysfunction in iSCI patients.

The objectives of our randomized controlled trial study are the following:

Primary objective:

To assess the temporal efficacy of iTBS on gait functions in incomplete spinal cord injury patients by evaluating spatio-temporal, kinetic and kinematic parameters.

Secondary objectives:

To assess the level specific gait deviations in different phases of gait cycle in incomplete SCI patients.

To examine the neurogenic lower urinary tract dysfunction following iTBS in incomplete SCI patients by evaluating urodynamic parameters.

The results from this study will serve as a starting point in better understanding common gait deviations and dyssynergia in bladder functions in Indian populations of iSCI and prospectively unmask a vivid evidential picture by manifesting the therapeutic efficacy of iTBS adjunct to physical rehabilitation if any. Ultimately on performing a successful trial, this management strategy will add quality instead of adding days to life in SCI patients.

Methods

Design

Patients with iSCI will be screened as per the inclusion and exclusion criteria (Table 1) and randomized into three groups. Demographics and basic medical assessment, gait analysis, urodynamics, neurological, functional, and psycho-social assessment will be done at baseline, after two weeks of intervention, and at follow-up periods. All the parameters will be measured at different temporal paradigms of the trial to avoid risk of urinary tract infection due to recurrent invasive procedure and feasibility and discomfort of patient while recording gait parameters. To observe the long-term sustainable effects of TMS along with physical rehabilitation, follow up will be done at 12 weeks. An overview of experimental design and outcome measures framework is illustrated in Fig. 1 and Table 2.

Table 1
Inclusion and exclusion criteria for screening of SCI patients.

Inclusion criteria	Exclusion criteria
1. SCI by traumatic or non-traumatic events 2. iSCI involving cervical (C5, C6, C7), thoracic and lumbar spine (AIS C or D). 3. Age range: 18–60 years 4. Duration: SCI ≤2 years	1. History of osteoporotic fractures or other pathological fractures 2. History of neurological diseases related to the spinal cord; congenital malformations (any disorder of neuro lesions) pertaining to CNS or PNS 3. History of seizures. 4. Patients with a cardiac pacemaker, deep brain stimulator, spinal cord stimulator, baclofen pump, or any ferromagnetic metallic implants close to the target stimulation area 5. Ventilator-dependent and intubated patients 6. Patients with cognitive impairments 7. Pregnant women 8. Acute eczema or bed sore under the target stimulation area

iSCI = Incomplete Spinal Cord Injury; CNS = Central Nervous System; PNS = Peripheral Nervous System.

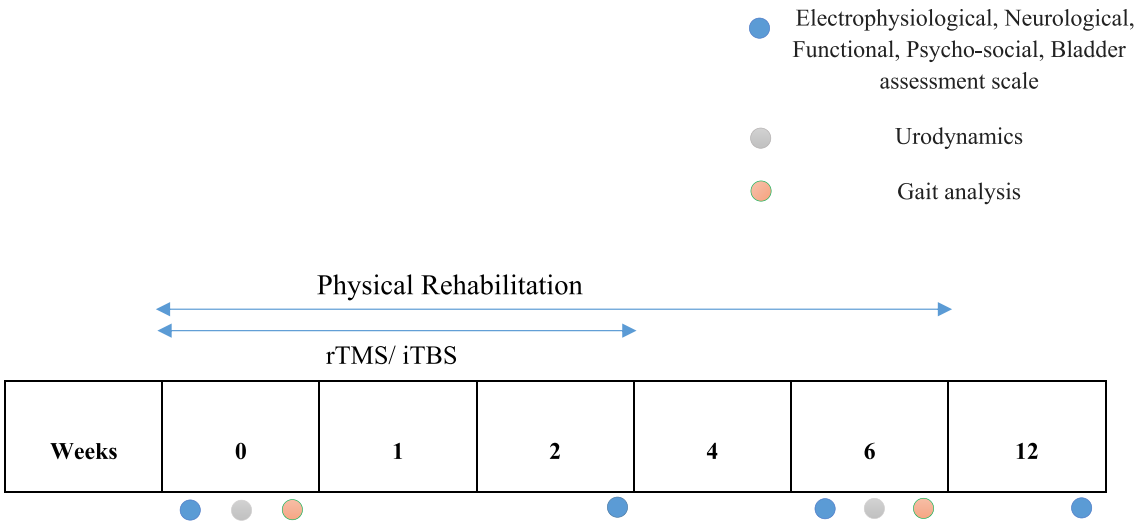

Fig. 1. Study design: Study timeline showing each study visit and the duration of the entire study. rTMS/ iTBS: 20 sessions will be delivered (2 sessions /day; 5days/week; for 2 weeks). rTMS = repetitive transcranial magnetic stimulation; iTBS = intermittent theta burst stimulation.

Table 2
Outcome measures recorded at different time points of the study.

	Total study period				
Outcome measures	Baseline	2nd week	4th week	6th week	12th week
Gait analysis & surface EMG of LL key muscles	✔			✔	
Urodynamics	✔			✔	
Bladder function assessment scale (NBSS)	✔	✔	✔	✔	✔
Electro physiological parameters (MEP, RMT, AMT, CSP)	✔	✔	✔	✔	✔
Neurological parameters (AIS, MAS)	✔	✔	✔	✔	✔
Functional parameters (WISCI II, SCIM III)	✔	✔	✔	✔	✔
Psychosocial parameters (BDI, STAI II, WHOQOL-BREF)	✔	✔	✔	✔	✔

EMG= Electromyography; LL = Lower limbs; NBSS= Neurogenic Bladder Symptom Score; MEP= Motor Evoked Potential; AMT= Active Motor Threshold; RMT= Resting Motor Threshold; CSP = Cortical Silent Period; AIS= American Spinal Cord Injury Association Impairment Scale; WISCI II= Walking Index for Spinal Cord Injury II; SCIM III = Spinal Cord Independence Measure III; BDI= Beck depression inventory; STAI II= State-Trait Anxiety Inventory II; WHOQOL-BREF= World Health Organization Quality of Life Brief Version.

Recruitment

Patients will be recruited from the Department of Neurosurgery and Orthopaedics, All India Institute of Medical Sciences (AIIMS), New Delhi admitted between September 2023 until August 2025. Informed, voluntary, and written consent will be taken from all participants before recruitment into the study. Participants will be given a choice to withdraw from the study at any given point in

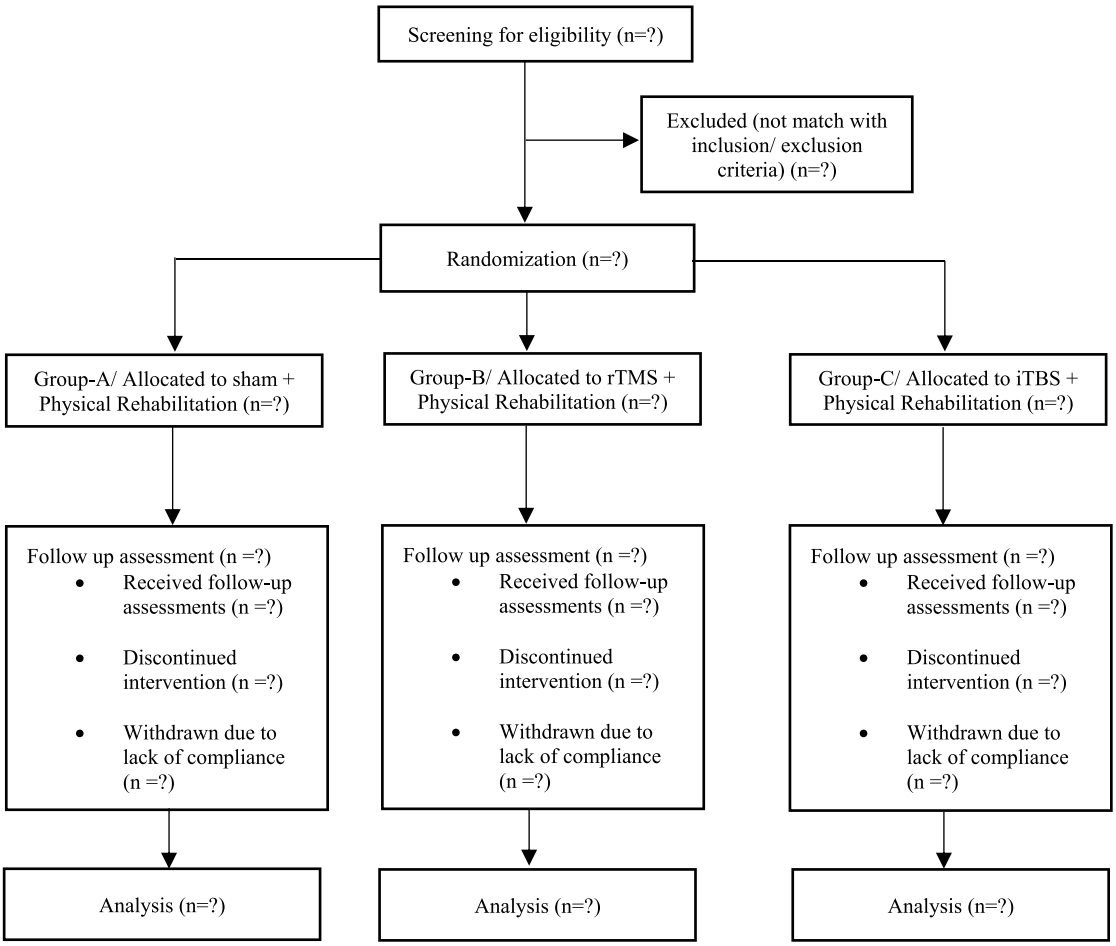

Fig. 2. Trial flow chart following CONSORT. rTMS = repetitive transcranial magnetic stimulation; iTBS = intermittent theta burst stimulation.

time. They will be duly informed of the duration and requirements of the study along with any potential risks or side effects associated with TMS intervention.

Blinding

A double-blind (investigator and patient), prospective, randomized, placebo-controlled study will be conducted. Blinding will be done by a person not involved in recording, evaluation and analysis of parameters.

Groups

Patients will be randomly assigned to 3 groups: Group A (sham stimulation + physical rehabilitation), Group B (rTMS + physical rehabilitation), and Group C (iTBS + physical rehabilitation). To allocate patients to these groups, a lab technician who will be masked and not part of this research will perform assignments based on a computer-generated random number. This trial's conduct and report will follow the Consolidated Standards of Reporting Trials (CONSORT) statement for Randomized Trials [15] (Fig. 2).

Intervention

The intervention protocol is designed based on previous studies conducted in incomplete SCI patients, predominantly focusing on motor deficits and ambulatory capacity [13,16–19]. Briefly, application of magnetic stimulation will be performed using an angulated figure of 8 coil (75 mm, Neurosoft MS/D), placed on the vertex using compatible neural navigation system, at 45° angulation. It will be directed postero-anteriorly, targeting cortical representation of the lower limbs in the primary motor cortex (M1) [20]. MEP will be recorded by a compatible electromyography system (Neuro-EMG-MS) using Ag-AgCl surface electrodes from the dominant side of contralateral tibialis anterior. Bi-phasic single pulses will be given to quantify RMT and determined by the minimum stimulator

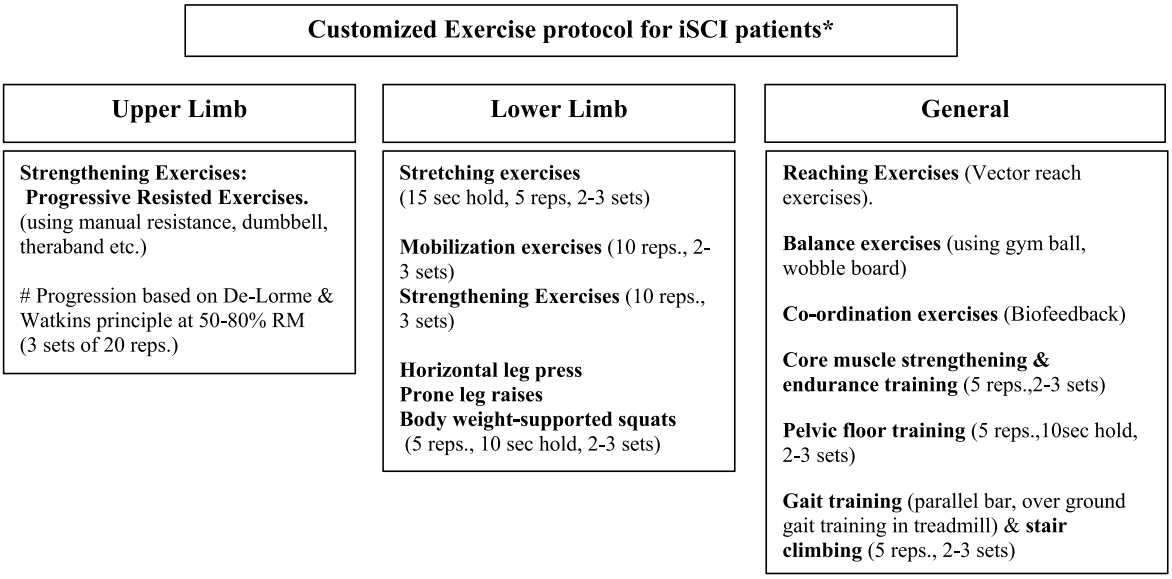

Fig. 3. Outline of physical rehabilitation regime for spinal cord injury patients. *Exercise prescription and progression will be based on individual's performance and tolerance to baseline exercises. iSCI = Incomplete Spinal Cord Injury.

intensity capable of eliciting MEPs of ≥50 μV amplitude in at least 5 out of 10 trials. rTMS will be consisted of 40 pulses of 2-*sec* bursts with an inter-burst interval of 28 s at 20 Hz, for a total of 1800 pulses over~20 min. The stimulation intensity will be set at 90 % resting motor threshold (RMT) [18]. iTBS will consist of 3-pulse bursts at 50 Hz repeated at 5 Hz. A 2-s train of theta bursts will be repeated every 10 s for 20 repetitions, for 600 pulses in total. 80 % RMT will be used as the iTBS intensity [17]. Group-A will receive placement of coil on the motor cortex, mimicking the exact sound but the coil will be disconnected from the power source. Group-B will receive active high-frequency rTMS and group-C will receive active high-frequency iTBS as described above.

The duration of each rTMS and iTBS session will be 20 min and 3 min 20 s respectively. Both rTMS and iTBS will be administered for a total of 20 sessions over a period of 2 weeks (5 days/ week, 2 sessions per day, 2 h inter session interval).

All the patients were screened for TMS checklist (history of seizure, metallic, dental or ferro magnetic implant in the body, history of chronic headache, open wound etc.) prior to intervention. During and after each session the patient was asked for any adverse symptoms viz; unwanted muscle twitch (eye, face), headache, nausea, vomiting, dizziness etc. Sudden appearance of any of the adverse symptoms or discomfort led to termination of stimulation without any delay.

Physical rehabilitation

A group of experienced Physiotherapists under the guidance of a concerned Spine surgeon is involved in developing a customized exercise regime for spinal cord injury patients. Based on current scientific guidelines for adults of spinal cord injury by Martin Ginis et al. [21] 2020 the team formulated tailored exercises regime compliant to: the level of injury and individuals' tolerance to perform grades of exercises. The complexity of an exercise regime graduated day by day upon the improvement in different domains (muscle strength, balance, walking speed, endurance, and functional independence). Exercises will be performed for 5 days/ week for 6 weeks for a duration of 30–45 min/session (Fig. 3).

Complete regime includes: 1. resisted training and range of motion exercises; 2. bed mobility exercises; 3. lower limb exercises; 4. balance and co-ordination exercises; 5. endurance training and functional exercises; 6. pelvic floor muscle training; and 7. gait training, treadmill training and stair climbing.

Pilot study

After obtaining due ethical clearance, we conducted a pilot study on two iSCI patients with motor deficits in lower limb and impaired bladder function. While one patient received iTBS, other received rTMS as per the mentioned protocol adjunct to physical rehabilitation. All the parameters and follow up studies were conducted as described in the manuscript. During and after each session patients were asked for any adverse or sudden appearance of any of the adverse symptoms. Both the patients did not report any adverse effects throughout the study and were comfortable with 2 sessions/ day for a total of 20 sessions.

Primary outcome

Gait analysis

Three-dimensional gait analysis will be done using Helen and Hayes protocol [22]. 18 spherical markers will be set in specific bi-lateral anatomical locations of the body (e.g., spinous process of C7 vertebra, acromion, ASIS, spinous process of second sacral vertebra, lateral mid of thigh connecting hip and knee joint line, lateral epicondyle of the knee, lateral mid of leg connecting lateral epicondyle of knee and lateral malleolus, lateral malleolus of ankle, calcaneal tuberosity and at 1st meta tarso phalangeal joint). Spatio-temporal, kinematic, and kinetic data will be captured and interpreted through video cameras, and force platforms in the gait lab. Surface electromyography will be used for evaluating the muscle activity of key muscles in the major joints of lower limbs (hip flexors and extensors, knee flexors and extensors, ankle dorsi, and plantar flexors) in iSCI patients. Any alternation or deviation of parameters will be compared with healthy control at baseline and after intervention in SCI patients. This method is highly reliable and valid [23].

Secondary outcomes

Bladder assessment parameters

Urodynamics is a highly reliable and valid technique and often considered the gold standard for assessing bladder function [24]. To objectively measure Neurogenic Lower Urinary Tract Dysfunction (NLUTD) in iSCI patients, specific parameters (i.e., incontinence abdominal leak point pressure, detrusor leak point pressure, cystometric capacity, maximum cystometric capacity, detrusor sphincter dyssynergia, post-void residual volume, bladder sensation, and compliance, etc.) will be studied [25,26].

Neurogenic bladder symptom scores (NBSS): require less time to complete, SCI patients can quickly answer all the questions. It consists of 23 questions and an additional 1 question on quality of life focuses on the patient's satisfaction with bladder function graded from 0 (pleased) to 4 (unhappy). Further, 23 questions are subdivided into 3 domains- incontinence; storage and voiding; consequences. Each question scores minimally 0 and maximally 3 or 4. The maximum score of each domain is 29, 22, and 23 respectively. Therefore, a total maximum 74 (maximum symptoms), and a minimum 0 (no symptoms at all) can be scored. For all domains, a higher score represents a worse symptom. This scale is highly reliable (ICC=0.85–0.86) and valid with good internal consistency (0.85) [27].

Electrophysiological parameters

Motor Evoked Potential (MEP) reflects the integrity of motor pathways and is often used to test both the conduction and excitability of the corticospinal system [28]. This method will be performed using a TMS coil on the primary motor cortex region (M1). MEP > 50 μV will be accepted for resting motor threshold and 100 μV or 200 μV will be considered as active motor threshold (AMT) [29].

Motor Threshold (MT) is a measure of cortical excitability expressed in percentage (%) as maximal stimulator outcome. RMT reflects the neuronal membrane threshold while active motor threshold (AMT) indicates the number of axons that are close to the firing threshold [30]. RMT will be determined when the target muscle is at rest and AMT will be obtained while the target muscle is actively contracted ~10–15 % MVC. The minimum stimulator intensity needed to elicit an MEP of 50 μV for RMT and 100–200 μV for AMT in at least 5 out of 10 trials will be considered [31,32].

Neurological parameters

American Spinal Injury Association Impairment Scale (AIS): International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) recommended AIS to be used specifically in SCI for assessing dermatomal superficial sensory examination (pinprick, light touch) and myotomal motor examination (using manual muscle technique for key muscles of upper and lower limbs). Sensory scores ranges from 0 (no sensation), 1 (impaired sensation) and 2 (intact sensation). Sensory scores are summed to give a total possible score of 224 (112 on each side). Motor score ranges 0–5 as per medical research council grading (no contraction to the full range of motion against gravity and maximal external resistance). A total maximum of upper and lower extremity motor score is 50 (25 on each side, each limb) [33]. A greater score for both sensory and motor function reflects a better prognosis of SCI patients. This scale also grades complete injury (AIS A) and incomplete injury (AIS B, AIS C, and AIS D) [34].

Modified Ashworth Scale (MAS): MAS evaluates hypertonicity of affected muscles efficiently in iSCI patients. The grades of spasticity are 0 (normal muscle tone), 1 (slight increase in muscle tone, during movement of limbs), 2 (more marked increase in muscle tone, but limb easily flexed), 3 (considerable increase in muscle tone), and 4 (limb rigid in flexion or extension). A lower score indicates greater recovery. This scale has excellent validity and reliability ($r = 0.95$) [35].

Functional parameters

Walking index for SCI II (WISCI II): This scale measures the type and amount of assistance (requirements of assistive devices, or human helpers) required to walk in acute and chronic SCI patients. The severity of walking impairment can be judged depending on the distance covered by the patient with the type and amount of assistance. This ordinal scale grades the extent of walking impairment;

from being unable to walk to independent walking. WISCI II consists of 21 levels. Level 0 on the scale signifies an inability to walk, level 20 signifies independent walking without any devices, orthotic support, and assistance. This scale demonstrates excellent reproducibility, having an intra-class correlation coefficient of 0.99 and high intra-rater (1.0) and inter-rater reliability (0.98) [36].

Spinal Cord Independence Measure III (SCIM III): SCIM III is only a comprehensive ability rating scale, designed to assess performance in activities in daily living especially for SCI patients. SCIM III has eliminated intra-cultural bias, thus becoming highly reliable and valid. It is divided into three domains: self-care, respiration and sphincter management, and mobility. Each domain is further divided into subparts e.g., self-care includes feeding, bathing, dressing, and grooming. The maximum score for the self-care domain is 20, the respiration and sphincter management domain is 40 and the mobility domain is 40. The lowest score is 0 signifying total assistance, and the maximum score is 100 indicating maximal independence [37].

Psycho-social parameters

Beck depression inventory (BDI): BDI, a 21-question multiple-choice self-report inventory, used to evaluate the presence and severity of depression often associated with SCI patients [38]. Each question score ranges from 0 to 3. A total score of 10 indicates normal, 11–16 indicates mild depression, 17–20 indicates borderline clinical depression, 21–30 indicates moderate depression, 31–40 indicates severe depression, and > 40 indicates extreme depression. iSCI patients who scored 9 or lesser are termed the “non-depressive group,” and those who scored 10 or more are termed the depressive group [39].

State-Trait Anxiety Inventory (STAI): STAI is a commonly used measure of trait and state anxiety. STAI consists of 40 questions, each question scores 1 (almost never), 2 (sometimes), 3 (often) and 4 (almost always) [40]. It can be used to diagnose anxiety and to distinguish from depressive syndromes. In SCI patients STAI acts as an indicator to rule out caregiver distress [41]. All outcome measures will be evaluated at baseline prior to intervention, post intervention and at 4th, 6th and 12th week from baseline except for gait analysis and urodynamics that will be evaluated at baseline and at 6th week.

World Health Organization Quality of Life Brief Version questionnaire (WHOQOL-BREF): It is a widely used generic health-related quality of life measure for patients with SCI across the globe. WHOQOL-BREF questionnaire is developed in the context of four domains defining quality of life viz: physical, psychological, social and environmental. It is a 26-item version of WHOQOL-100 assessment [42]. Each item has a minimum score of 1 and maximum of 5. The higher the score, the higher the livelihood satisfaction. The questionnaire is suitable for measuring QOL in spinal cord injury patients and has good internal consistency (0.74–0.78) [43].

Statistical analysis

Data will be presented as Mean and standard deviation (SD). The intention-to-treat (ITT) analysis will be the primary analysis. Baseline observation will be carried forward for subjects with missing values. Unless otherwise stated, ITT data will be presented throughout. Per-protocol analysis (all compliant participants) will also be conducted. One-way ANOVA will be used to compare differences in mean values between the three groups at baseline and post-intervention. A paired *t*-test will be used to compare the pre and post-intervention mean values within the group. The difference between the three groups post-intervention will also be presented. P value < 0.05 at (95 % CI) will be considered statistically significant. Statistical analysis will be done using STATA 14.0 (STATA Corp, Houston, TX, USA) software.

Power calculation and sample size

The number of patients required for this study will be calculated a priori to ensure sufficient statistical power. Power estimation will be based on an earlier study done by Feng et al. (2023) using walking speed as one of the primary outcomes [13]. Walking speed was 0.8 ± 0.25 in the sham group and 1.25 ± 0.20 in the intervention group. Setting α value at 0.05 and power of study at 90 % and using the above values in the two-tailed formula for sample size calculation, using G* power software (version 3.0.10) we get a sample size of 7 subjects in each group. Adjusting for a possible 30 % dropouts, the sample size comes to 10 in each group. Therefore, the total sample size will be a minimum of 30 subjects.

Discussions

Our study focuses on improving ambulation in spatiotemporal, kinetic, and kinematic components and restoring urodynamic parameters in iSCI after employing iTBS and rTMS interventions and comparing the effects of iTBS and rTMS. Preclinical studies in complete and incomplete rat models of spinal cord injury have shown significant beneficial effects of external magnetic field exposure for 5–8 weeks on autonomic (urinary bladder) function, locomotion, sensorimotor and pain perception. The functional recovery observed is suggested to be due to attenuation of glial scaring, lesion volume, neurotransmitter imbalance and facilitation of neuronal survival and axonal regeneration (Pal et al. 2013, 2018; Dey et al. 2017; Bhattacharyya et al. 2020; Kumar et al. 2021) [44–48]. Application of iTBS for 2 weeks has also shown to facilitate cortical excitability and promote axonal regeneration in SCI rat model (Marufa et al. 2021) [49]. In an iSCI rat model, significant improvement in motor function is seen by coupling active rTMS therapy and treadmill training for 5 days/ week up to 8 weeks [50]. In parallel domain, a study conducted in motor incomplete spinal cord injury patients, demonstrates improvement in gait function (as assessed by step length, cadence, timed up and go test and 10-meter walk test) and decrease in spasticity following cortical rTMS intervention coupled with physical rehabilitation for 15 sessions over 3 weeks [16]. In a randomized controlled trial, improved lower limb muscle strength and recovery of ambulation has

reported after application of high-frequency rTMS (20 Hz for 20 sessions) associated with long-term exercise training in SCI patients [19]. In incomplete spinal cord injury patients, intermittent theta-burst stimulation along with physiotherapy of 5 sessions/ week for 9 weeks promoted lower extremity motor recovery [13]. All these studies suggest significant improvement in motor function and ambulation in SCI patients after rTMS therapy in conjuction with physical exercise training. Previously, only a single randomized controlled trial reported, few sub domains of spatio-temporal parameters after rTMS intervention in incomplete SCI [51]. However, no study has reported kinetic, kinematic and spatio-temporal joint-specific (mainly at hip, knee, and ankle) impairments of lower limbs in SCI patients and its improvement after rTMS or iTBS intervention. But no study has reported kinetic, kinematic, and spatio-temporal joint-specific (mainly at hip, knee, and ankle) impairments of lower limbs in SCI patients and its improvement after rTMS or iTBS intervention. We believe this novel study will add to the colossal knowledge of gait alterations in SCI patients.

A significant improvement in bladder function in terms of generation of voluntary urine, bladder capacity, post-void residual urine has been reported following spinal magnetic stimulation for 16 weeks [52]. However, we did not find any reports evaluating the effect of cortical application of rTMS/ iTBS on pathogenesis of bladder function in SCI patients, the present study is an unique work with respect to the assessment of urinary bladder recovery after iTBS therapy.

Further, in SCI patients, earlier studies had investigated the sustainable effect of rTMS or iTBS intervention only for either 2 (Benito et al. [16]) or 4 weeks (Kumar et al. [18]) follow up as the research design evolved. In present study, the TMS intervention will be given for 2 weeks and thereafter to facilitate and maintain the effects of TMS, the physical rehabilitation program will be continued for further 4 weeks (i.e. until 6 weeks), as also reported by Kumru et al. 2016 [18]. Thereafter, to observe the long-term sustainable effects of TMS along with physical rehabilitation, we plan to do 2nd follow up at 12 weeks. In stroke patients also follow up studies has been done until 12 weeks to observe maintenance of recovery [53,54].

The biggest advantage of using iTBS over classical rTMS is the smaller intervention time that enables the patients to increase tolerance against any symptoms (like pain) related to spinal cord injury. Moreover, according to the study of Huang et al., (2005), iTBS has shown to have a greater and stronger stimulus effect lasting more than one hour compared with traditional rTMS [55]. Finally, rehabilitation plays an important role to execute any purposeful movement through motor planning, learning, and relearning [56,57]. Therefore, we hypothesize to establish iTBS and physical rehabilitation as a most effective, standard treatment regime for SCI patients. Though in literature transient mild headache and facial muscle twitch which disappears spontaneously soon after intervention has been reported, during standardization procedure and in pilot trial using present protocol, the SCI patients did not report any of the adverse effects.

Limitations

We planned to administer 20 sessions to SCI patients as suggested by Kumru et al., (2016) [18]. However, we observed that most of the spinal cord injury patients coming to our hospital has severe financial constraints and their residence is in other cities, thus we will administer 2 sessions/ day at an interval of two hours. To ensure effectiveness, safety and tolerance, we conducted the above-mentioned pilot study and did not observe any adverse effects. Further, Modirrousta et al., (2018) has shown that application of rTMS, twice session daily (after an interval of $\geq$ 15 min) is tolerable, safe, and as effective as conventional single session [58]. The trial limitation also includes measurement of urodynamics and gait analysis only once post-intervention, due to potential risks of urinary tract infection during catheterization and high cost of test procedure respectively.

Ethics and dissemination

This study will be conducted in accordance with the Declaration of Helsinki and is consistent with Good Clinical Practice Guidelines. The study is ethically approved by the Institute Ethics Committee of AIIMS, New Delhi (IECPG-312/07.06.2023, RT-10/20.07.2023) and registered with the Clinical Trials Registry-India (CTRI) (CTRI/2023/08/056,150). We undertake that the requested regulatory approvals are taken for the study. The results of this trial will be presented at various national and international scientific forums and will be published in peer-reviewed journals. Additionally, a summary of the trial findings will be updated in the CTRI portal. Each patient will receive customized feedback upon completing the trial.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Rohit Banerjee: Conceptualization, Data curation, Investigation, Writing – original draft. **Deeksha Patel:** Data curation, Methodology. **Kamran Farooque:** Investigation, Writing – review & editing. **Deepak Gupta:** Methodology, Writing – review & editing.

Amlesh Seth: Supervision. **Kanwal Preet Kochhar:** Writing – review & editing, Supervision. **Bhavuk Garg:** Investigation. **Siddharth Jain:** Methodology. **Nand Kumar:** Methodology, Investigation. **Suman Jain:** Conceptualization, Supervision, Writing – original draft.

Data availability

No data was used for the research described in the article.

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