

BRIEF REPORT

Trans-Spinal Theta Burst Magnetic Stimulation in Parkinson's Disease and Gait Disorders

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ABSTRACT: Background: Gait disorders in patients with Parkinson's disease (PD) can become disabling with disease progression without effective treatment.

Objectives: To investigate the efficacy of intermittent θ burst trans-spinal magnetic stimulation (TsMS) in PD patients with gait and balance disorders.

Methods: This was a randomized, parallel, double-blind, controlled trial. Active or sham TsMS was applied at third thoracic vertebra with 100% of the trans-spinal motor threshold, during 5 consecutive days. Participants were evaluated at baseline, immediately after last session, 1 and 4 weeks after last session. Primary outcome was Total Timed Up and Go

(TUG) values comparing active versus sham phases 1 week after intervention. The secondary outcome measurements consisted of motor, gait and balance scales, and questionnaires for quality of life and cognition.

Results: Thirty-three patients were included, average age 68.5 (6.4) years in active group and 70.3 (6.3) years in sham group. In active group, Total TUG mean baseline was 107.18 (95% CI, 52.1–116.1), and 1 week after stimulation was 93.0 (95% CI, 50.7–135.3); sham group, Total TUG mean baseline was 101.2 (95% CI, 47.1–155.3) and 1 week after stimulation 75.2 (95% CI 34.0–116.4), $P = 0.54$. Similarly, intervention had no significant effects on secondary outcome measurements. During stimulation period, five patients presented with mild side effects (three in active group and two in sham group).

Discussion: TsMS did not significantly improve gait or balance analysis in patients with PD and gait disorders. The protocol was safe and well tolerated. © 2024 International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease/parkinsonism; gait disturbance/ataxia; surgery/stimulation; all spinal cord

Eighty-one percent of Parkinson's disease (PD) patients develop dopamine non-responsive axial problems 15 years after disease onset.¹ In particular, freezing of gait (FOG) impairs mobility, affecting 7% of patients in early PD, and ~60% in advanced stages.² Although dopaminergic medications and deep brain stimulation (DBS) significantly ameliorate cardinal motor symptoms in PD, their effects on gait and balance are less predictable and not well sustained in the long-term.³ Rehabilitation programs have shown improvements in gait and balance disorders; however, their long-term effectiveness remains uncertain.⁴

Given high prevalence of gait and balance problems in PD and limitations of the currently approved therapies, researchers have explored alternative strategies such as electrical spinal cord stimulation (SCS). SCS is a well-established therapy for treatment of chronic pain resulting from various pathologies^{5,6} and has been applied in small cohorts of patients with PD, showing positive effects.⁷ The hypothesis is that neuromodulation caused by SCS may induce excitation of dorsal column pathways⁸ and could lead to cortico-striatal desynchronization⁹ and may also have a neuroprotective effect.^{10,11} However, it is limited by requirement of invasive implantation of epidural stimulation.

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Trans-spinal magnetic stimulation (TsMS) is an emerging method that can affect spinal circuitry noninvasively and has shown promise in alleviating motor symptoms of PD, with the benefit of safety and cost in comparison to SCS.¹² Following a previous pilot study showing positive effects of TsMS in patients with PD and gait disorders,¹³ we report here a phase II clinical trial on the effects of intermittent θ -burst (iTBS) TsMS on gait, balance, and other motor symptoms.

Methods

Trial Design

This randomized, parallel, double-blind, controlled trial was conducted at the University of São Paulo to evaluate the efficacy of iTBS TsMS in patients with PD and gait disorders. This study was approved by the Institutional Review Board of the University of São Paulo (CAPPesq:16233819.8.0000.0068) and registered as NCT04783493 at clinicaltrials.gov.

Participants

Eligible participants were adults between 21 and 80 years who met the following inclusion criteria: (1) idiopathic PD whose primary symptoms included gait and/or balance alteration (score ≥ 1 on sub-item 2.12 of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale [MDS-UPDRS]); (2) presence of FOG (score ≥ 1 in sub-item 2.13 of the MDS-UPDRS); (3) mini-mental state examination ≥ 24 points; and (4) able to give informed consent. Exclusion criteria: (1) uncontrolled psychiatric comorbidities; (2) active infection or other untreated conditions; (3) pregnancy; (4) concurrent other experimental drugs; (4) cardiac pacemakers and/or electronic devices; (5) chronic pain in lower limbs; and (6) inability to walk without assistance.

Interventions

A circular (MCF-125) coil with static cooling (Magventure, Denmark) connected to a MagPro20 machine (MagVenture, Farum, Denmark) in contact with skin, was placed at level of third thoracic vertebra at midline, with cable pointing to right side. A figure-of-eight (B-65) coil with active cooling (Magventure, Denmark) was positioned 15 cm behind patient using a mechanical arm. These two coils were used during sessions of all patients. Stimulation intensity was set to 100% of trans-spinal motor threshold (TsMT), determined by palpation of abdominal contraction. In the sham group, the same process for obtaining the TsMT through abdominal contraction was mimicked, but no pulses were applied.

In the active group, the circular coil was turned on and the figure-of-eight coil was left off. Stimulation

protocol was adapted from the pilot study¹³ and consisted of iTBS with 20 trains of stimulation of 20 bursts each at 5 Hz; each burst was composed of 3 pulses at 50 Hz, totaling 1200 pulses. An interval of 8 seconds between trains was used, with total session length of 3 minutes and 52 seconds. In the sham group, the circular coil was turned off, and figure-of-eight coil was turned on, with the same setup applied in active group. Patients remained seated during stimulation.

To create a sensation of muscle contraction and improve blinding, transcutaneous electrical nerve stimulation (Neurodyn Portable TENS, Ibramed) was performed in both groups,¹⁴ with no neuromodulatory effect once the time is less than 20 to 30 minutes.¹⁵ Two pairs of stimulation stickers placed parallel, laterally on both sides at second and third thoracic level, programmed parameters: 80 Hz, 150 ms, and ~ 60 mA (Supplementary Fig. S1).

All patients underwent intervention for five consecutive days and were assessed at baseline, immediately after the last session, 1 and 4 weeks after the last session. Patients were requested not to change rehabilitation or medication throughout the study.

Gait Outcomes Measurement

Primary outcome measure was the change in Total TUG test between baseline and 1 week after intervention, comparing active and sham groups. Total TUG was calculated by adding best time of three attempts to turn right with best time of three attempts to turn left.^{16,17} Secondary outcomes were changes between baseline and post-intervention in Balance Evaluation System Test (BESTest), Unified Parkinson's Disease Rating Scale part III (UPDRS-III), dual-task TUG, percentage of FOG (%FOG, calculated from total duration of FOG during Total TUG test),¹⁸ FOG score, New Freezing of Gait Questionnaire (NFOG-Q), Parkinson's disease Questionnaire 39 (PDQ-39) and Frontal Assessment Battery (FAB). A sole-blinded movement disorder specialist performed all tests for different scales.

Randomization and Masking

Eligible patients were randomly assigned in a 1:1 ratio to active or sham stimulation using computer-generated pairwise randomization according to order of enrolment and stratification with a blocking scheme (block size of six or four). A randomization sequence was revealed only to unmasked clinician responsible for stimulation programming. Patients were blinded to randomization and were never scheduled at same time; therefore, they were not able to exchange information in waiting room.

Stratification was performed using value of the TUG test applied to identify patients with PD who are at risk

for falls, with a cut-off score of 11 seconds for discrimination of those who did or did not fall.¹⁹ Therefore, patients with TUG values <33 seconds were allocated to mild group, whereas those with TUG values ≥33 seconds to severe group.

Statistical Analysis

Based on a pilot study,¹³ we designed the study to have an overall power of 80% to detect a 55% reduction in primary endpoint in active stimulation group and a 30% reduction in sham stimulation group, with an α error of 0.05, with 17 participants per group. For primary and secondary endpoints, a generalized estimating equation approach with an unstructured correlation matrix was used to estimate the overall interaction between treatment and time as well as pairwise comparisons for each specific time point. Safety analyses were conducted using the χ^2 or Fisher's exact tests. Analyses were performed using SPSS

Statistical Software (Version 26.0. Armonk, NY: IBM Corp) or Software (Version 4.1.2, R Core Team, 2022).

Data Sharing

Anonymized data from this study will be shared by request from any qualified investigator.

Results

Forty participants were assessed for eligibility between July 2021 and December 2021, enrolling 35 participants. Eighteen patients were randomly assigned to sham group and 17 to active group. Two participants were excluded from final analysis (one from active withdrew after sessions because of infection of central nervous system from a previous neurosurgery, and one withdrew from sham because of difficulty

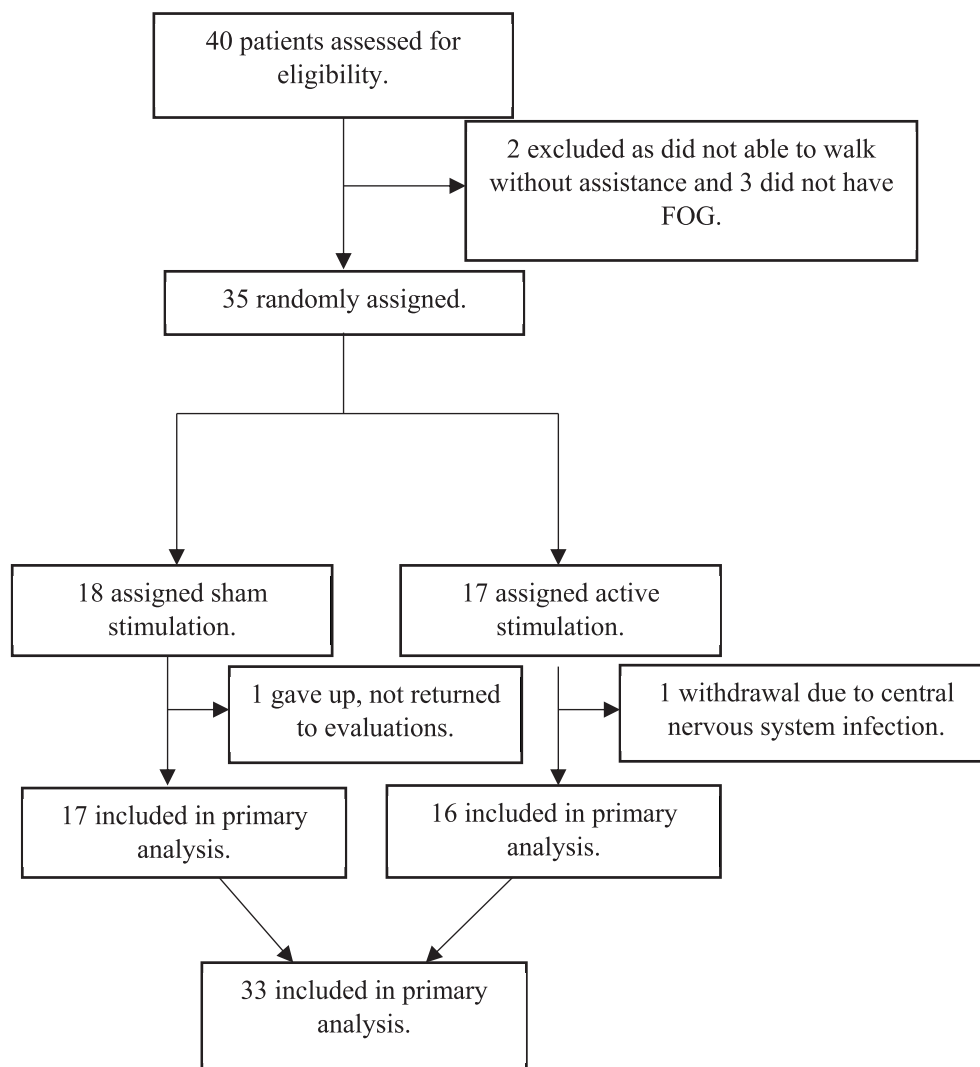
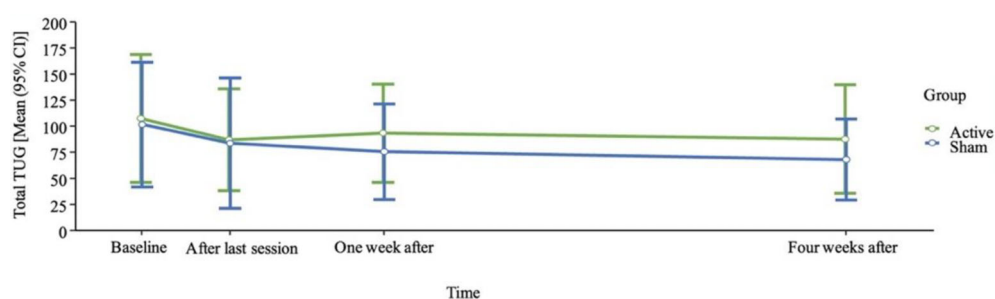


FIG. 1. Trial profile.

TABLE 1 Description of the overall study sample

Variables	Active (n = 16)	Sham (n = 17)	P-value
Age (y) (mean ± SD)	68.56 (6.4)	70.3 (6.3)	0.42
Disease duration (y) (95% CI)	9.0 (5.7–11.2)	7.0 (4.0–13.0)	0.69
Time since first gait complaint (y) (95% CI)	3.5 (2.0–7.0)	3.0 (2.0–4.0)	0.33
Rehabilitation program (2 times/week; 1 h/session)	6 (37.5%)	12 (70.5%)	0.05
Total TUG (seconds) (95% CI)	53.0 (40.7–120.5)	50.00 (42.00–78.00)	0.90
BESTest (95% CI)	70.1 (61.5–78.7)	72.3 (60.9–83.8)	0.77
Dual task TUG (seconds) (95% CI)	59.0 (46.2–99.7)	62.50 (52.50–93.50)	0.93
FOG Score (95% CI)	12.0 (6.7–24.0)	10.00 (6.00–15.75)	0.50
UPDRS III (mean ± SD)	50.4 (13.6)	43.8 (12.3)	0.15
NFoG-Q (95% CI)	19.5 (14.0–22.2)	21.00 (17.0–22.0)	0.49
PDQ-39 (95% CI)	39.0 (27.2–51.6)	42.3 (35.2–48.0)	0.66
FAB (95% CI)	16.0 (14.7–18.0)	16.0 (14.0–18.0)	0.76

Abbreviations: SD, standard deviation; CI, confidence intervals; TUG, Timed Up and Go test; BESTest, Balance Evaluation System Test; FOG, freezing of gait; UPDRS III, Unified Parkinson's disease Rating Scale part III; NFOG-Q, New Freezing of Gait Questionnaire; PDQ-39, Parkinson's disease Questionnaire 39; FAB, Frontal Assessment Battery.

**FIG. 2.** Analysis of Total Timed Up and Go (TUG) values at baseline, after the last session, one week after and four weeks after the last session in the active and sham groups.**TABLE 2** Primary outcome total TUG (seconds) (95% CI)

Time	Active group	Sham group	Difference	P-value
Baseline	107.18 (52.17–162.17)	101.22 (47.10–155.35)	−5.95 (−83.12 to 71.21)	0.880
After last session	86.53 (42.71–130.35)	83.22 (26.77–139.68)	−3.31 (−74.77 to 68.16)	0.928
One week after the last TsMS session	93.06 (50.78–135.34)	75.2 (34.01–116.44)	−17.84 (−76.88 to 41.21)	0.554
Four weeks after the last TsMS session	87.24 (40.57–133.90)	67.56 (32.59–102.52)	−19.68 (−77.99 to 38.63)	0.508

Overall interaction P -value = 0.74. P -values obtained from generalized estimating equations – interactions between group (active or sham) and time. Abbreviations: TUG, Timed Up and Go test; CI, confidence intervals; TsMS, Trans-spinal magnetic stimulation.

in attending evaluations). The study was completed by 33 participants (17 in sham group and 16 in active group) (Fig. 1). Demographic and clinical characteristics were similar between groups, except for the adherence to rehabilitation (two or more sessions per week, lasting 1 hour or more per session) (Table 1).

Change in the Total TUG test between beginning and 1 week after stimulation was not significantly different between groups. In active, Total TUG mean at baseline was 107.18 (95% CI, 52.1–116.1), and 1 week after stimulation was 93.0 (95% CI, 50.7–135.3); in sham, Total TUG mean baseline was 101.2 (95% CI, 47.1–155.3) and

TABLE 3 Secondary outcomes

Variables	Active				Sham				P-values	
	Baseline	After last session	1 week after last session	4 weeks after last session	Baseline	After last session	1 week after last session	4 weeks after last session	After last session	1 week after last session
BESTest (95% CI)	70.1 (61.5–78.7)	73.9 (65.3–82.6)	76.6 (69.3–83.9)	76.9 (69.5–84.3)	72.3 (60.9–83.8)	77.3 (66.5–88.2)	81.0 (70.2–91.8)	81.5 (70.4–92.6)	0.77	0.52
UPDRS III (95% CI)	50.1 (44.0–56.2)	43.5 (37.2–49.8)	46.1 (40.6–51.6)	41.2 (35.8–46.7)	43.3 (37.9–48.8)	43.6 (37.6–49.6)	43.1 (37.7–48.4)	42.1 (36.4–47.8)	0.10	0.97
FOG score (95% CI)	15.7 (10.4–20.9)	15.4 (10.0–20.8)	15.6 (10.8–20.5)	15.2 (10.2–20.1)	13.7 (9.0–18.3)	13.1 (8.7–17.5)	14.5 (9.5–19.5)	14.5 (9.81–19.3)	0.58	0.50
FOG % (95% CI)	20.0 (8.9–31.1)	19.6 (8.5–30.8)	22.7 (10.4–35.1)	18.3 (8.4–28.2)	21.4 (12.1–30.6)	19.1 (10.2–28.1)	15.3 (6.3–24.3)	15.6 (7.2–24.0)	0.85	0.94
Dual TUG (s) (95% CI)	100 (53.1–148.4)	84.7 (45.5–124.0)	87.1 (52.9–121)	79.2 (41.5–116)	97.3 (58.8–135)	73.1 (51.1–95.0)	72.0 (51.7–92.3)	66.1 (50.7–81.6)	0.91	0.61
PDQ-39 (95% CI)	41.5 (32.0–51.0)	34.4 (26.7–42.2)	35.3 (26.6–43.9)	41.5 (32.0–51.0)	42.0 (35.9–48.1)	38.4 (32.3–44.5)	39.1 (33.0–45.3)	42.0 (35.9–48.1)	0.92	0.43
FAB (95% CI)	15.5 (14.2–16.8)	16.3 (15.2–17.5)	16.5 (15.7–17.4)	17.0 (16.3–17.7)	15.7 (14.1–17.3)	16.1 (14.8–17.4)	16.2 (15.0–17.5)	16.9 (15.7–18.1)	0.89	0.78
NFoG	18.9 (16.4–21.4)	18.0 (14.8–21.1)	18.3 (15.0–21.6)	18.5 (15.1–22.0)	19.9 (18.2–21.6)	18.7 (16.6–20.8)	20.0 (17.9–22.0)	21.0 (16.5–20.3)	0.51	0.70

P-values obtained from generalized estimating equations – interactions between group (intervention or control) and time.

Abbreviations: BESTest, Balance Evaluation Systems Test; CI, confidence interval; UPDRS III, Unified Parkinson's Disease Rating Scale part III; FOG score, Freezing of Gait score; FOG %, Freezing of Gait percentage; TUG Dual task, Timed Up and Go test dual task; PDQ-39, Parkinson's disease Questionnaire 39; FAB, Frontal Assessment Battery; NFoG-Q, New Freezing of Gait Questionnaire.

1 week after stimulation was 75.2 (95% CI, 34.0–116.4), $P = 0.54$. Interaction between group difference in the mean change in the Total TUG value and times showed no statistical significance ($P = 0.74$) (Fig. 2, Table 2). There was no significant difference in changes in secondary outcomes (Table 3).

Five patients presented mild side effects (three in active group and two in sham group) such as drowsiness, insomnia, and urinary incontinence and did not persist.

Blinding Assessment

At the end of the study, all patients could tell which protocol of treatment they received, and 21 patients (62.85%) did correctly, 13 (59.09%) were in sham and eight (40.91%) were in active ($P = 0.11$).

Discussion

In this randomized, double-blind, sham-controlled trial, we observed no significant reduction in gait impairment, balance, or PD motor symptoms between sham and active TsMS groups during the double-blind period. Although the safety of technique was demonstrated with no serious side effects, the lack of positive findings from stimulation contrasts with previous findings.^{13,20}

Another recent study also explored TsMS in PD with positive effects on UPDRS III and TUG test, using similar parallel settings, with two arms of 50 subjects.²⁰ Methodological differences could account for distinction in outcomes. Unlike this study, intensive rehabilitation was coupled with TsMS, possibly attaining greater rehabilitation effectiveness from combination with neuromodulation, as documented in spinal cord injury recovery with SCS²¹ and treadmill training with transcranial magnetic stimulation.²² The stimulation period and session intervals were also different, with 4 weeks of biweekly stimulation, perhaps benefiting from a putative cumulative effect. Mitsui's study was single blinded, the superior findings might stem from our blinding protocol.²⁰ Placebo effect of patients with PD is well observed in several trials, occurring in up to 59% of patients²³ and dependent on patient confidence in therapy effectiveness.²⁴

Patient selection might also have played a role in lack of response to TsMS, as observed in SCS.⁷ Similar to DBS, selection of a good responder depends on the response of motor symptoms to levodopa treatment,²⁵ and a subgroup of selected patients might respond better to therapy.

Putative mechanism of TsMS in PD would be similar to SCS,⁷ either by direct dorsal column stimulation or by synchronous activation of several tactile afferents, mostly at multiple dorsal roots.¹² Because we defined stimulation intensity by motor root stimulation, intensity might not have been sufficient to properly activate afferents or spinal

cord tracts. The selection of the upper thoracic level was inspired by previous invasive SCS studies conducted at this level, which reported improvements in gait and FOG in PD.²⁶ Nevertheless, this might not necessarily be the optimal spot. There is currently no consensus about the best location for electrode implantation in SCS or for administering non-invasive stimulation. Future studies might consider exploring other targets, with lumbar levels standing out as a promising alternative because of their potential to stimulate the lower limb tracts more effectively at the roots. The safety profile of TsMS and low cost allow for further exploration with an improved study and stimulation design. ■

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.
J.R.M. – study concept, design, acquisition and interpretation of data, literature search, writing of manuscript.
G.A.N. – acquisition and interpretation of data, literature search, critical revision of manuscript.
R.B.C. – study concept, design, acquisition and interpretation of data, literature search, writing of manuscript.
J.d.S.S. – acquisition and interpretation of data, literature search, critical revision of manuscript.
D.J.F.S. – study concept critical, revision of manuscript.
J.R.O. – study concept critical, revision of manuscript.
M.J.T. – study concept critical, revision of manuscript.
M.A.M. – study concept, design, acquisition and interpretation of data, literature search, writing of manuscript.
E.R.B. – study concept critical, revision of manuscript.
C.T. – study concept critical, revision of manuscript.
D.C.d.A. – study concept critical, revision of manuscript.
R.G.C. – study concept, design, acquisition and interpretation of data, literature search, writing of manuscript.

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