



Short communication

Transcutaneous magnetic spinal cord stimulation for freezing of gait in Parkinson's disease



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ABSTRACT

Dopaminergic drugs partially alleviate gait problems in Parkinson's disease, but the effects are not sustained in the long-term. Particularly, the freezing of gait directly impacts patients' quality of life. Experimental epidural spinal cord stimulation (SCS) studies have suggested positive effects on locomotion among PD patients, but the effects of non-invasive stimulation have never been explored. Here, we investigated in a prospective, open-label, pilot study the efficacy and safety of non-invasive magnetic stimulation of the spinal cord in five patients with PD who experienced gait problems, including freezing of gait. A trial of transcutaneous magnetic SCS was performed at the level of the fifth thoracic vertebra. The primary outcome was the change in freezing of gait 7 days after stimulation. Secondary outcome measures included changes in gait speed and UPDRS part III. After non-invasive spinal cord stimulation, patients experienced a 22% improvement in freezing of gait ($p = 0.040$) and 17.4% improvement in the UPDRS part III ($p = 0.042$). Timed up and go times improved by 48.2%, although this did not reach statistical significance ($p = 0.06$). Patients' global impression of change was 'much improved' for four patients. Improvement in gait after stimulation was reversible, since it returned to baseline scores 4 weeks after stimulation. No severe side effects were recorded. This pilot study suggests that transcutaneous magnetic spinal cord stimulation is feasible and can potentially improve gait problems in PD, without severe adverse effects. Large scale phase II trials are needed to test this hypothesis.

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1. Introduction

Gait disorders are among the most prevalent problems in the advanced phase of Parkinson's disease (PD) and are relatively resistant to dopaminergic treatment [1]. Freezing of gait (FoG) affects 7% of patients in early PD and reaches 60% in advanced stages [1]. The current treatment of FoG involves a multidisciplinary approach with physiotherapy and pharmacological strategies [2]. However, the effects of that treatment remain partially efficacious [3], probably reflecting its multifaced and enigmatic underlying pathophysiology [2].

A positive effect of epidural spinal cord stimulation (SCS) on locomotive activity has been reported in animal models and small

cohorts of PD patients and seems to be promising [4]. Transcutaneous SCS is an emerging method that activates similar target neural structures noninvasively, and has recently been explored to the treatment of spasticity after spinal cord injury [5]. Here, we investigated the safety and efficacy of transcutaneous magnetic SCS on FoG and other motor symptoms in a cohort of PD patients.

2. Methods

Five patients (two females and three males, 68.8 ± 7.1 years) were included in this prospective, open-label, pilot study. Eligibility criteria included: i) idiopathic PD with III or IV scores on Hoehn & Yahr scale; and ii) presence of moderate FoG (Unified Parkinson's Disease Rating Scale [UPDRS] part III Fog subscore of 2 or greater) as the most bothersome symptom, despite optimized clinical treatment. The protocol was applied to patients after at least 12 h without parkinsonian drugs (off-state). This study was approved by the

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local ethics committee and registered at Clinical Trials.gov (NCT04171076). All patients provided informed consent.

A trial of transcutaneous magnetic SCS was performed with a figure-of-eight coil (Magventure® MagPro® R20) at the level of the fifth thoracic vertebra. The coil was placed perpendicular to the spinal cord. The stimulation intensity was set at 90% of motor threshold (fifth thoracic nerves contraction). Each stimulation session consisted of 20 theta-burst trains at 5 Hz, with 20 pulses each at 50 Hz, for a total of 400 pulses throughout 2 min. Patients received three sessions with a 60 min interval.

Gait was assessed through the new freezing of gait questionnaire (NFOG, considering FoG symptoms over the last week) and timed up and go test. Patients underwent a motor score evaluation (UPDRS-III), which was determined under off-medication and best on-medication conditions 1 week before the stimulation. After stimulation, the UPDRS-III was performed during off-medication. Measurements were recorded at baseline, immediately after the stimulation session, 7 days after stimulation, and 28 days after stimulation (to test a loss of benefit over time).

The primary outcome was the change in NFOG 7 days after stimulation. Secondary outcome measures included changes in TUG and UPDRS-III immediately and 7 days after stimulation, and patients' global impression of change 7 days after stimulation. The Wilcoxon signed-rank test was used to detect significant changes for each variable. Significance was set at $p < 0.05$.

3. Results

The patients revealed improvement in freezing of gait and other motor symptoms 7 days after SCS (Fig. 1 and Table 1), which tended to return to baseline scores at the final evaluation (28th

day, $p > 0.05$). Seven days after stimulation, new freezing of gait questionnaire improved by 22% ($p = 0.040$) and UPDRS-III by 17.4% ($p = 0.042$) compared with baseline. Timed up and go was numerical – but not significantly – better after stimulation (improvement by 48.2%, $p = 0.060$). Patients' global impression of change was 'much improved' for four patients and 'minimally improved' for one patient. No severe side effects were recorded. One patient reported fatigue in the abdominal region just after stimulation, which was self-limited. There were no limb weakness or urinary incontinence along the follow-up period. Video 1 illustrates the effects of SCS on two patients.

4. Discussion

In this pilot trial, transcutaneous magnetic SCS improved gait parameters in patients with PD, with no associated severe side effects. The improvement was reversible, since there was no carry-over effect 28 days after stimulation. Moreover, the improvement was consistent, since, in four out of five patients, the global impression of change was "much improved". To our knowledge, this is the first study to report the effect of non-invasive magnetic stimulation over the spinal cord on gait in a cohort of PD patients.

Few clinical studies of PD patients have demonstrated positive results of epidural SCS on abnormal posture and gait disturbances [6–8]. Here, we tested a novel paradigm of stimulating the spinal cord noninvasively through a transcutaneous magnetic field. We targeted the fifth thoracic level because of our previous positive experience with dorsal epidural spinal cord stimulation [8]. In order to verify adequate dorsal columns stimulation, we based the stimulation intensity on anterior musculature response, thus

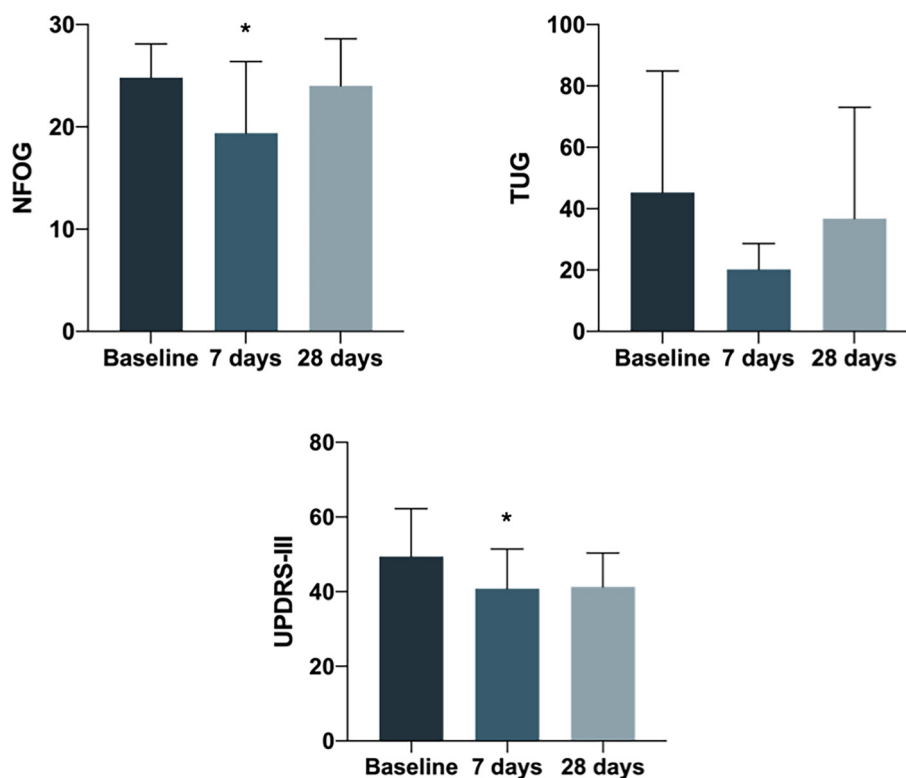


Fig. 1. Effects of transcutaneous magnetic spinal cord stimulation on gait measures along the study. * Seven days after stimulation, the freezing of gait and the UPDRS-III significantly improved comparing to baseline. Gait speed (TUG) was numerical – but not significantly – better after stimulation. The measures after 28 days were not different statistically from the baseline, showing the reversibility of the effect. NFOG, new freezing of gait questionnaire; TUG, Timed up go test; UPDRS-III, Unified Parkinson's Disease Rating Scale part III. Results are shown in means and standard deviation. Video 1. Video shows the patients 1 and 2 performing gait tasks before and after the transcutaneous magnetic spinal cord stimulation.

Table 1
Gait and motor assessment before and after stimulation.

Patient	Age (y)/Sex	NFOG baseline	NFOG 7 days*	NFOG 28 days	TUG baseline	TUG immediately after stimulation	TUG 7 days	TUG 28 days	UPDRS-III baseline	UPDRS-III after stimulation	UPDRS-III 7 days	UPDRS-III 28 days	LEDD (mg/d)	Disease Duration (y)
P1	62/M	28	26	26	104	34	25	100	57	50	45	42	1300	17
P2	65/F	28	26	28	69	34	32	34	61	52	52	49	1230	20
P3	73/M	24	9	16	10	8	10	12	31	35	29	34	1050	8
P4	79/M	24	17	24	21	34	18	19	57	49	48	51	675	7
P5	65/F	20	19	26	24	19	16	19	41	28	30	30	1275	8
Average ± SD		24.8 ± 3.3	19.4 ± 7.1	24.0 ± 4.7	45.6 ± 39.6	25.8 ± 11.8	20.2 ± 8.5	36.8 ± 36.2	49.4 ± 12.8	42.8 ± 10.6	40.8 ± 10.6	41.2 ± 9.1	1106 ± 260	11.8 ± 6.2
P value compared with baseline		-	0.040	0.593	-	0.225	0.060	0.104	-	0.080	0.042	0.080	-	-

P, Patient; F, female; M, male; NFOG, new freezing of gait questionnaire; TUG, Timed-Up-Go Test; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; SD, Standard deviation. * Primary outcome.

ensuring sufficient stimulation depth and making the paradigm more robust.

The mechanisms accounting for the effect of SCS in PD are unknown, but from accumulated experience in animal models, it has been proposed that stimulation of afferent pathways within the dorsal columns ascending to mesencephalic locomotor facilitates the initiation of movement [9]. Additionally, in a primate model of PD, the motor improvement after SCS was strongly associated with the desynchronization of aberrant low-frequency synchronous corticostriatal oscillations (beta-band power), in a manner that mimics the effects caused by pharmacological dopamine replacement therapy or deep brain stimulation [9].

This pilot study aimed to explore the safety and fundamentally of stimulating the spinal cord through theta-burst magnetic stimulation. Due to the small sample size and explorative paradigm, the statistical analysis should be interpreted with caution. Additionally, at this time, a placebo effect cannot be ruled out as this was an unblinded pilot, although that most of the patients' impression was that the best response was perceived only after 2 days makes this less likely. The most important finding was that the procedure seems to be safe and can, somehow, influence FoG and gait speed during the short term after stimulation, returning to the baseline over time. Most importantly, the impression from the patients of change was consistent. A phase II trial should be performed to validate these preliminary findings.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jocn.2020.10.001>.

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