Burst Transspinal Magnetic Stimulation Alleviates Nociceptive Pain in Parkinson Disease-A Pilot Phase II Double-Blind, Randomized Study

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BURST TRANS-SPINAL MAGNETIC STIMULATION ALLEVIATES NOCICEPTIVE PAIN IN PARKINSON'S DISEASE - A PILOT PHASE II DOUBLE-BLIND, RANDOMIZED STUDY

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Abstract:	Background and aims: Nociceptive is the most prevalent pain mechanism in Parkinson disease (PD). It negatively affects quality of life and there is currently no evidence-based treatment for its control. Burst spinal cord stimulation has been used to control neuropathic pain, and recently shown to relieve pain of nociceptive origin. Here, we hypothesize that burst trans-spinal magnetic stimulation (bTsMS) reduce nociceptive pain in PD. Materials and Methods: Twenty-six patients were included in a double-blind, sham-controlled, randomized parallel trial design, and the analgesic effect of lower-cervical bTsMS was assessed in patients with nociceptive pain in PD (NCT04546529). Five-daily induction sessions were followed by maintenance sessions delivered twice a week for seven weeks. The primary outcome was the number of responders (≥ 50% reduction of average pain intensity assessed on a numerical rating scale ranging from 0-10) during the 8 weeks of treatment. Mood, quality of life, global impression of change, and adverse events were assessed throughout the study. Results: Twenty-six patients (46.2% women) were included in the study. The number of responders during treatment was significantly higher after active compared to sham bTsMS (p = 0.044), mainly due to the effect of the first week of treatment, when eight (61.5%) patients responded to active and two (15.4%) responded to sham bTsMS (p=0.006); number needed to treat=2.2 at week 1. Depression symptom scores were lower after active (4.0±3.1) compared to sham bTsMS (8.7±5.3; p=0.011). Patient's global impressions of change were improved after active bTsMS (70.0%) compared to sham bTsMS (18.2%; p=0.030). Minor adverse events were reported in both arms throughout treatment sessions. One major side effect unrelated to treatment occurred in the active arm (death due to pulmonary embolism). Blinding was effective. Conclusion: bTsMS provided significant pain relief and improved the global impression of change in PD in this phase-II trial.

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RUNNING HEAD: Burst-TsMS for Parkinson Pain

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Authorship Statement:

Daniel Ciampi de Andrade and Jorge Dornellys da Silva Lapa conceived and designed the study. Jorge Dornellys da Silva Lapa, Pedro Henrique Martins da Cunha, Vitor Macedo Brito Medeiros, and Adriano Donizeth Silva de Morais conducted patient examinations and collected clinical data. Jorge Dornellys da Silva Lapa, Daniel Ciampi de Andrade, Pedro Henrique Martins da Cunha, Vitor Macedo Brito Medeiros, and Ana Mércia Fernandes provided intellectual input in analyzing the data and performed statistical analyses. Jorge Dornellys da Silva Lapa and Daniel Ciampi de Andrade drafted the manuscript. Thomas Graven-Nielsen, Manoel Jacobsen Teixeira, and Rubens Gisbert Cury revised the manuscript for critically important intellectual content.

Conflicts of interest

No conflict of interest to be reported.

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ABSTRACT

Background and aims: Nociceptive is the most prevalent pain mechanism in Parkinson disease (PD). It negatively affects quality of life and there is currently no evidence-based treatment for its control. Burst spinal cord stimulation has been used to control neuropathic pain, and recently shown to relieve pain of nociceptive origin. Here, we hypothesize that burst trans-spinal magnetic stimulation (bTsMS) reduce nociceptive pain in PD.

Materials and Methods: Twenty-six patients were included in a double-blind, sham-controlled, randomized parallel trial design, and the analgesic effect of lower-cervical bTsMS was assessed in patients with nociceptive pain in PD (NCT04546529). Five-daily induction sessions were followed by maintenance sessions delivered twice a week for seven weeks. The primary outcome was the number of responders (≥ 50% reduction of average pain intensity assessed on a numerical rating scale ranging from 0-10) during the 8 weeks of treatment. Mood, quality of life, global impression of change, and adverse events were assessed throughout the study.

Results: Twenty-six patients (46.2% women) were included in the study. The number of responders during treatment was significantly higher after active compared to sham bTsMS ($p = 0.044$), mainly due to the effect of the first week of treatment, when eight (61.5%) patients responded to active and two (15.4%) responded to sham bTsMS ($p=0.006$); number needed to treat=2.2 at week 1. Depression symptom scores were lower after active (4.0±3.1) compared to sham bTsMS (8.7±5.3; $p=0.011$). Patient's global impressions of change were improved after active bTsMS (70.0%) compared to sham bTsMS (18.2%; $p=0.030$). Minor adverse events were reported in both arms throughout treatment sessions. One major side effect unrelated to treatment occurred in the active arm (death due to pulmonary embolism). Blinding was effective.

Conclusion: bTsMS provided significant pain relief and improved the global impression of change in PD in this phase-II trial.

Keywords: Parkinson disease, chronic pain, spinal cord, neuromodulation, trans-spinal magnetic stimulation, burst, nociceptive pain, musculoskeletal pain, spinal cord stimulation

1. INTRODUCTION

Despite having been reported since the original description of Parkinson disease (PD), non-motor symptoms (NMS) remained underexplored for a long period(1). Recently, there has been a steady increase in the interest on NMS since they are currently known to substantially impact functioning and quality of life in PD(2). Of the several NMS, pain is often reported by PD patients at all stages of disease. Pain has a large and important negative impact on quality of life even in early-stage disease(3)(4)(5)(6).

PD is a multisystemic disease and its associated pathological findings can be identified in extranigral regions including non-dopaminergic systems(7)(8)(9). Indeed, some NMS are dopamine-responsive, while others are not. Dopamine-replacement therapy may not alleviate all NMS and specific treatments may be necessary to improve quality of life of patients experiencing NMS(10)(11). Dopaminergic treatment improves pain in only some PD patients, and there is no correlation between motor improvement and pain relief after dopaminergic or neuromodulatory treatments(11)(12). Pain in PD is often underassessed, and nearly half of patients do not receive medications or physical therapy. This is partially due to the lack of assessment tools validated to classify pain in PD as well as due to limited evidence-based treatment options. Current recommendations do not distinguish among different pain types in PD and they acknowledge the paucity of treatment options supported by evidence(10).

Chronic pain (pain lasting for more than three months and present most of the days) affects 18% of the general population(13)(14). Chronic pain is present in 20% of PD patients in the early stages of the disease but up to 80% of patients in later stages(3)(15)(16). PD pain is divided into pain unrelated to PD and pain related to PD. The later refers to chronic pain aggravated by PD or de novo pain appearing during disease installation, while PD-unrelated pain refers to previous chronic pain that is not

influenced by PD(17). PD-related pain is further classified according to the International Association for the Study of Pain mechanistic classification and subsequent validation studies into nociceptive, neuropathic, and nociplastic pains syndromes(18). PD-nociceptive pain is the most frequent pain type and is present in 55% of the patients. It is more commonly located in the trunk and the lower back regions and is often localized or regional(17). It is associated with levodopa-induced dyskinesia, thus clustering away from neuropathic and nociplastic pain types in PD(17).

Spinal cord stimulation is a long-known treatment option for neuropathic pain. It was initially believed its effects stemmed from dorsal column-mediated effects and pain gate-control mechanisms(19), while it was later shown to have a much wider effect in spinal cord information processing, affecting extra-lemniscal tracts, including structures located in the anterior portions of the spinal cord(20). Lately, new evidence has shown that burst spinal cord stimulation can lead to lower back and axially located pain relief possibly due to its enhanced effects on wide dynamic range (WDR) cells. A preferential influence on medial nociceptive pathways leading to modulation of the affective dimension of pain has also been put forward(21)(22). Indeed, pain relief was shown to be higher in surgically-implanted burst stimulation compared to conventional continuous unpatterned stimulation in well-designed studies(23). This led us to conduct a pilot double-blind parallel trial to test the safety and potential analgesic effects of burst trans-spinal magnetic stimulation (bTsMS) in PD-related nociceptive pain. We hypothesized that the benefits of spinal cord stimulation obtained in non-neuropathic or mixed pain syndromes could be reproduced by non-invasive stimulation to the same spinal segments by an induced electric current delivered by TsMS.

2. METHODS

2.1 Patients

Our Institution's Ethics Review Board approved this study (#36024620.8.0000.0068), which was registered on clinicaltrials.gov (NCT04546529). PD patients with chronic nociceptive pain related to the disease were recruited from outpatient movement disorders clinics geographically near the outpatient pain clinics of the Hospital das Clínicas, University of São Paulo, between July 2020 and May 2021(13). Idiopathic PD was diagnosed based on the 2015 Movement Disorder Society (MDS) clinical diagnostic criteria(24). Nociceptive pain was diagnosed according to the Parkinson disease pain classification system (PD-PCS) by two independent researchers and reviewed by an expert(17). All patients provided informed consent to participate in the study.

The inclusion criteria were adults (18-85 years) with PD-related nociceptive pain persisting for more than 3 months and present most of the days. The average pain intensity (24h) score had to be ≥ 4/10 on a numerical rating scale (NRS). Exclusion criteria were pregnancy, breast feeding women, presence of defined chronic neuropathic pain according to the IASP grading system for neuropathic pain and a positive DN-4 (Douleur Neuropathique-4 questionnaire), previous diagnosis of dementia, known major psychiatric disorders (as assessed by the DSM-V), history of substance abuse, or work litigation issues(17)(25)(26). Demographic and clinical information about the patient was collected at the inclusion visit including physical examination to confirm PD and the presence of nociceptive pain.

2.2 Experimental design

This was an exploratory randomized, double-blind, sham-controlled, and pilot parallel trial to investigate the analgesic effects of active versus sham bTsMS in nociceptive PD-related chronic pain.

Participants were allocated into groups that either received burst trans-spinal magnetic stimulation (bTsMS) in a prolonged continuous theta burst stimulation or sham stimulation over the seventh cervical vertebra (C7) in the midline. They were randomly assigned to groups in a 1:1 ratio (using https://www.random.org/sequences), and the randomization sequence was stored in a sealed opaque envelope and was only revealed to the researchers responsible for the administration of bTsMS, and who had no other role in the study and were not allowed to interact with patients except for strictly stimulation-related communications.

Patients underwent active or sham bTsMS sessions for eight weeks. In the first week, stimulation sessions were performed daily for five consecutive days (induction series) followed by two sessions weekly (maintenance series) for seven more weeks. Patients were followed for four additional weeks after the last treatment session for safety and assessed on until the 12th week from study initiation by a phone call.

2.3 Burst trans-spinal magnetic stimulation

The trans-spinal resting motor threshold (tsRMT) was determined before the first session with patients positioned in an armchair, relaxed, in a sound-attenuated room using a single pulse TMS pulse (ie, edge of the circular coil) over the C7 vertebral segment with a circular-shaped coil (MCF-125 coil with static cooling, MagVenture, Farum, Denmark) connected to a MagProX100 machine (MagVenture, Farum, Denmark). Trans-spinal motor-evoked potentials (MEP) were recorded using surface electrodes (Natus,

Middleton, WI, USA) located on the lower abdominal muscle (3rd lower bellies of rectus abdominalis muscles). The trans-spinal rest motor threshold (ts-RMT was defined as the lowest intensity eliciting a detectable motor-evoked potential in 5 out 10 trials. The stimulation intensity for the bTsMS was set at the detection threshold of tsRMT.

Two different coils were used for the treatment sessions. In all instances, a circular-shaped coil was positioned over the spinous process of the 7th cervical vertebra with the cable pointing to the side, with the induced electric current flowing lateral form medial in the spinal cord. A figure-of-eight (B-65) coil with active cooling (Magventure, Farum, Denmark) was placed orthogonally to circular-shaped coil. For real stimulations, the circular coil in contact with the skin was turned on, and the figure of eight coil was left off. Stimulation was delivered by three pulses at 50 Hz and repeated 400 times with an inter-stimulus interval of 200 milliseconds; 1,200 pulses were delivered per session over 1 minute and 20 seconds(27). For sham sessions, the same set up was used except that the circular coil was turned off while the figure-of-eight coil was turned on and delivered stimulation at 100% of maximal stimulator output. The figure-eight coil was placed on the circular-shaped coil to ensure proper double-blinded conditions. The figure-of-eight coil is supposed to provide the noise and vibration related to the stimulation, but would have no specific biological effect on the spinal cord since its several centimeters away from the skin. The coils were fixed by a mechanical arm, and the position was systematically controlled during the session. Additionally, in all sessions, a transcutaneous electric stimulation system was mounted over both sides of the circular coil touching the skin at the C7 level before the start of stimulation. The two carbon rubber surface electrodes were placed 5 cm from the coil edges on each side in a longitudinal orientation (Figure 1). Biphasic square wave impulses at a frequency of 100 Hz and pulse duration of 50 μs were used during both active and sham bTsMS session (Neurodyn

Portable TENS, Ibramed). The stimulation intensity was increased until there was local paresthesia without discomfort. Stimulation was started and stopped time-locked to bTsMS.

2.4 Pain and related assessments

A full clinical and pain assessments were performed at baseline and after and eight (last) weeks. Pain intensity and adverse events were also assessed at the first, second and fourth weeks, and one month after the last stimulation session, this time by a structured phone interview. The primary outcome of the study was the number of patients reaching significant average pain relief (≥50% pain intensity reduction) during the eight weeks of stimulation sessions versus baseline assessment. The average pain intensity over the past 24h was assessed by a numerical rating scale (NRS) (28) ranging from 0 (no pain) to 10 (maximal pain imaginable).

2.5 Secondary outcomes

Pain intensity and its frequency and severity were assessed by the composite score from PD-PCS(17). This score ranges from 0 (no pain) to 90 (maximal pain intensity, impact in activities and high frequency). Mood was assessed by the hospital anxiety and depression scale(29). Quality of life was assessed by EuroQol-5(30). Parkinson's disease motor symptoms were assessed by UPDRS part III(31). Pain interference in daily living was measured by the seven items from the short form of the brief pain inventory ranging from 0 (does not interfere) to 10 (maximal interference)(32). The global impression of change is a seven-point Likert scale that ranges the amount of improvement or aggravation after

a treatment. We compared percentage of subjects who reported much, and very much improvement after treatment against all the other options(33).

2.6 Adverse events report

The incidence of treatment-emergent adverse events and the safety of bTsMS were assessed by measuring the number of participants who experienced serious events. Adverse events assessment was performed after each treatment session by using a dedicated questionnaire(34). Patients were asked to report any potential side-effects related to the treatment such as headaches, dizziness, nausea, blurred vision, sleepiness, paresthesia, and local pain.

2.7 Blinding assessment

Care was taken not to set patients' appointments simultaneously so that waiting-room conversations were avoided and ensuring the integrity of blinding. The blinding assessment was performed at the end of the study (i.e., after eight weeks of treatment) as previously reported(34)(35), and included the following questions: i. could you tell which treatmet you received?"; ii. "If so, which was it?", iii. "If you were given the option to do so, would you choose to maintain the treatment for a longer period of time?".

2.8 Statistical analyses

The normality was verified by asymmetry and kurtosis values in addition to graphical methods(36). Categorical data were described using absolute and relative frequencies and compared through Fisher's exact test, and numerical data were described through median and quartiles and compared through Mann-Whitney's U test.

Longitudinal continuous data were analyzed through two-way repeated measures analysis of variance (ANOVA). For binary endpoints, generalized estimating equations were employed, as this approach allows considering participants with missing data on specific time points and therefore uses all available data without biasing the results under random dropouts(37)(38), so that data imputation strategies were not required. Treatment effects were estimated through group versus time interactions. All tests were two-tailed, and final p-values less than 0.05 were considered significant. All analyses were conducted using the Statistical Package for Social Sciences software (IBM SPSS Statistics for Windows, version 24.0. Armonk, NY: IBM Corp.). Since there are no other studies in the literature reporting non-invasive spinal cord stimulation for pain in PD, we included a convenience sample of PD based on previous studies using TsMS for other etiologies. Based on our findings we calculated the number necessary to treat, which will help future studies to properly estimate sample size.

3. Results

3.1 Sample description

Thirty patients were screened for participation, and twenty-six were randomized (Figure 2). Thirteen patients received active and 13 with sham bTsMS. Table 1 shows baseline demographic and clinical characteristics of the 26 patients that received the allocated interventions. The active bTsMS and sham bTsMS groups were similar in terms of baseline characteristics.

3.2 Pain assessment

Data from twenty-six PD patients were analyzed in an intention-to-treat approach. Pain intensity reduction ≥50% was higher after active bTsMS compared to sham bTsMS over the eight weeks of treatment (p=0.044) (Table 2). Pain intensity went from 6.2±1.7 and 7.0±1.3 at baseline to 2.4±2.2 and 3.9±2.6 on the eighth week of stimulation after the active and sham bTsMS series, respectively. At the end of the first week (the induction phase), eight (61.5%) responders to active bTsMS and two (15.4%) responders to sham bTsMS (p=0.006). The number needed to treat was 2.2 after the first week of treatment. Number of responders were no longer different between groups at 8 weeks and one month after the last stimulation day (P=0.120) (Table S1). We ran supplementary analyses to investigate differences in response to bTsMS being related to the location of the main pain syndrome. We dived patients according to the location of the main pain syndrome as being located above or below the spinal C7. There were no differences between predominant neck-shoulder-upper limb pain regions (i.e.., above C7 spinal cord level) and thoraco-lumbar-lower limb (below C7 spinal cord segment) pain regions with number of responders after first week (p=0.710) and the last week (p=0.218) of treatment.

3.3 Secondary outcomes

Depression scores were lower after active bTsMS (4.0±3.1) compared to sham bTsMS (8.7±5.3) ($p = 0.011$). Patient's clinical global impressions of change were more frequently much/moderately improved after active bTsMS (70.0%) compared to sham bTsMS (18.2%) (p=0.030) (Table S2). Other secondary outcomes are shown in Table 3.

There were no differences between groups concerning Parkinson motor symptoms severity (UPDRS part III), anxiety symptoms (HADS-A), pain interference in daily activities (BPI pain Interference on daily activities), quality of life (EQ-5D-3L total, and health score), BPI pain intensity index, and PD-PCS score (Table S3).

3.4. Dropouts and adverse events report

Four patients dropped out during the study. One left due to a lack of analgesic effects (after the 7th sham daily session) from the placebo group. In the active group, 3 patients dropped out of the study. One patient had dizziness that was aggravated after active stimulation that led to treatment interruption. One dropped out due to SARS-CoV 2 infection, and one had pulmonary embolism leading to death. Concerning adverse events that did not lead patients to drop out of study, two patients reported headache (one after 1 active stimulation session and one after 1 sham stimulation session) that did not persist until the next stimulation session, none of them needed analgesics. One had transient paresthesia after a one active stimulation session, one had dizziness after three sham stimulation sessions that did not need treatment, and one had transient blurred vision after two sham stimulation sessions. There were no other side effects such as seizures, nauseas, and drowsiness.

3.5 Blinding assessment

After the end of the study, 21 patients (95.5%) said they could tell which protocol of treatment they received, 13 patients (62.0%) guessed it correct. Of these patients, eight (72.7%) were in sham group, and five (50.0%) were in active group (p = 0.36). Twenty patients (95.2%) said they would like to maintain the sessions of bTsMS for a more extended period if this option were offered to them.

4. DISCUSSION

The present results show that bTsMS had a significant analgesic effect in PD patients with nociceptive pain within the first week. An overall effect was found during the 8 weeks of treatment, the most significant pain relief occurring after the first week of daily stimulation, with 61.5% responders in active bTsMS and 15.4% responders in the sham bTsMS group. As secondary outcome bTsMS also showed a reduction in depressive symptoms, and there was an improvement in the patient's clinical global impressions of change after treatment.

Even though we were able to detect an analgesic effect of non-invasive spinal cord stimulation in PD for the first time, one needs to acknowledge that dopaminergic medication and treatment states can influence pain perception and impact in PD patients in very dynamic manner. For example, PD patients in the off medication state have shown reduced non-painful mechanical and thermal and mechanical pain thresholds compared to healthy volunteers (3)(12)(39). Dopaminergic replacement and turning on deep brain stimulation systems can restore pain thresholds towards normal values, mainly due to modulation of small fiber-mediated sensory inputs(39)(40). These data suggest that PD patients have an inherent pro-nociceptive state that can be modulated by medication or neuromodulatory interventions primarily prescribed to treat motor symptoms. However, one recurrent finding in the PD literature is the lack of correlation between pain improvement with treatment prescribed for motor symptom control, suggesting that

dopamine replacement therapy and deep brain stimulation may act on motor and NMS by different mechanism, or on a group level, responders do not have the same degree of improvement in these two types of symptoms (41). In fact, for deep brain stimulation, it has been recently shown that slight differences in the volume of activated tissue within the subthalamic nucleus can influence different cortical networks and potentially explain different clinical motor and NMS effects after deep brain stimulation (39)(42)(43).

The control of PD-related pain is so far limited. In a study using high-frequency transcranial magnetic stimulation, modulation of the primary motor cortex was attempted to relieve musculoskeletal pain in PD, there were significant analgesic effects with active versus sham stimulation as well as impacts on motor symptom, mood symptoms, and overall disease severity(44). One open label study showed that duloxetine may be effective at treating pain in PD, but this result was not confirmed in a later double-blind, randomized, placebo-controlled trial(45)(46). Indeed, the phase II double-blind, randomized, placebo-controlled study did not show significant improvement of severe pain in PD with prolonged-release oxycodone–naloxone, while treatment-related nausea and constipation was more common in the active group than the placebo group(28). Epidural SCS was tested in a single arm, prospective, non-randomized case series to treat predominant neuropathic pain in PD patients. The electrodes were implanted in the cervical or thoracic spine level, and pain average scores decreased 59% in the burst stimulation group with better results. Basic gait analysis revealed mild improvement in motor symptoms(47).

In the present study we chose to focus on pain of nociceptive mechanisms, mainly due to PD-related chronic musculoskeletal pain, because it is the most frequent subtype in PD patients. Treatment options for nociceptive PD pain are rare(3)(17)(42)(48), and it causes significant negative impact in quality of life(17). Spinal neuromodulation is thought to

control pain through potential segmental and supraspinal mechanisms. In the early days of spinal cord stimulation, analgesic effects were believed to be caused by stimulation of large myelinated fibers on the dorsal columns, which would lead to pain reduction according to the pain gate control theory(19). It was latter shown that spinal cord stimulation influences the processing of several neurophysiological responses in the spinal cord, including autonomic and motor processing(20). This argued for a broader spread of the effects of the spinal electric field, which would be likely related to its analgesic mechanisms. Additionally, spinal cord stimulation has significant effects in vasomotor control, being used to treat peripheral chronic artery disease(51) and as a potential adjunct treatment of orthostatic hypotension in atypical parkinsonism syndromes(52). More recently, spinal stimulation with burst waves was shown not to influence the dorsal column activity directly, but lead to a major effect on wide-dynamic range neurons in the dorsal horn besides and distinct influence in medial spinothalamo-cortical pathways; suggesting that burst spinal stimulation can engage widespread suprasegmental structures, including the emotional pathways of pain processing(21)(53). In experimental studies, the spinal stimulation-mediated analgesia was related to increased release of inhibitory neurotransmitters, decreased wide-dynamic cells activity, and activation of rostroventral medulla with descending modulation of nociception(54)(55)(56). In human studies, it has been reported that SCS inhibits the nociceptive flexor reflex (RIII), which related to treatment efficacy. Additionally, decrease in cortical excitability (somatosensory evoked potential-SEP) and a reduction in thalamic-to-cingulate connectivity were also reported(20)(57).

There is still little knowledge regarding the mechanisms behind TsMS effects. Studies showed a reduction in corticospinal excitability (e.g., trans-spinal MEP) in healthy subjects(58)(59). Experimental studies showed that rats under a spinal cord injury model

undergoing TsMS had higher growth-associated protein-43, 5-hydroxytryptamine expression than sham rats receiving TsMS with potential benefits in motor function recovery(60). MEPs reduction was also described in TsDCS studies associated with reductions in SEPs(49)(61). Others have reported TsDCS led to increased intracortical facilitation(61)(62)(63). A TsDCS study with chronic pain patients showed anodal stimulation compared to sham decreases nociceptive flexor reflex (RIII) linearly with a reduction of pain scores(50). These data suggest that both invasive (SCS) and non-invasive trans spinal stimulation strategies engage segmental, supra segmental, and neuro-humoral responses, which may be related to its potential analgesic effects. However, more studies in chronic pain patients need to be conducted to ascertain if both approaches are similarly effective. Our results speak for a more widespread analgesic effect of bTsMS delivered to C7, since pain located below and above the stimulated spinal cord segment were similarly positively affected by treatment.

Minor adverse events were reported in active and sham groups. One directly led one patient to drop out of study in the active group. The single major side effect (death due to pulmonary embolism) was not considered to be specifically associated with active treatment. Spinal cord stimulation is used in patients with chronic arterial insufficiency and atherosclerosis as a mean to improve blood flow secondary to sympathetic-mediated arterial vasodilation of arterioles and is considered to be safe in vasculopathy and in patients at risk for atherothrombosis or arterial occlusion(64). However, venous vascular side effects need to be taken with caution and actively monitored in future studies.

Blinding is a major challenge in spinal cord stimulation studies, in particular non-invasive ones. We created an original strategy as an attempt to mitigate this potential source of

bias. Two coils were used during the stimulation setup. Both coils were present during all sessions. Similar strategies were employed in studies on transcranial magnetic stimulation(27)(65). Furthermore, active cutaneous electrical stimulation was used to mitigate unblinding. The efficacy of the blinding strategy suggests participants in the active group had a similar percentage of correct guessing in which group they were allocated to as patients from the sham arm.

There are several limitations in this study that should be noted. First, due to it is exploratory nature, it was primarily designed to explore the feasibility, and temporal profile of the technique in PD patients with pain. The effects found here will be valuable in the design of future studies, but smaller studies usually tend to overestimate treatment effects, and this needs to be taken into account when interpreting the results(66). Also, while we found an overall effect of active stimulation over the first eight weeks, this effect was only significant, and was mainly driven, by the period when stimulation was delivered daily, during induction sessions (i.e., after 1 week of treatment). That means that dosing remains to be determined for bTsMS, and one cannot currently know whether our maintenance sessions were adapted to maintain the effects seen after induction, or if these effects will only exist during daily stimulations, not being amenable to be sustained for longer periods of time by sessions spaced for more than one day. This distinction is central for a potential future use of the technique in clinical practice. Another point is that patients included in the study could have pain in body segments above the stimulation level (ie, C7). We decided to proceed with such a strategy based on several facts. One is that while the pain location can be located above C7, MSK pain commonly leads to referred pain, so that pain location and lesion site quite often do not coincide spatially. Additionally, pain of nociceptive nature in PD is mainly located axially, and in more than one site (17). Based on data suggesting the rather diffuse analgesic effects of burst spinal

cord stimulation, we hypothesized that the effects would not be segmentary restricted. However, while it is generally acknowledged that spinal cord stimulation may have suprasegmental neurophysiological effects, it is not known whether analgesic effects extend above the stimulation level in non-invasive trans-spinal approaches(67)(68)(69)(70). Our analyses comparing patients with predominant pain located above C7 and those with main pain located at body parts innervated by spinal cord segments below C7 were not different. Still, due to the exploratory nature of this study and its subsequent small sample, claims that bTsMS had diffuse analgesic effects need to be tuned down before larger samples are studied. Finally, this study had no mechanistic exploration of the effects of bTsMS. Neurophysiological, neuroimaging and psychophysical changes caused by bTsMS may provide valuable insights in following studies. In conclusion, this pilot trial suggests bTsMS provided analgesia predominately within the first week of daily sessions and was safe in nociceptive pain in PD. More studies are needed to deepen knowledge about this technique as an adjunct therapy to nociceptive pain.

REFERENCES

1. Jost WH, Reichmann H. “An essay on the shaking palsy” 200 years old. J Neural Transm. 2017;124(8):899–900.
2. Antonini A, Albin RL. Dopaminergic treatment and nonmotor features of Parkinson disease: The horse lives. Neurology. 2013;80(9):784–5.
3. Beiske AG, Loge JH, Rønningen A, Svensson E. Pain in Parkinson’s disease: Prevalence and characteristics. Pain. 2009;141(1–2):173–7.
4. Roh JH, Kim BJ, Jang JH, Seo WK, Lee SH, Kim JH, et al. The relationship of pain and health-related quality of life in Korean patients with Parkinson’s disease. Acta Neurol Scand. 2009;119(6):397–403.
5. Camacho-Conde JA, Campos-Arillo VM. The phenomenology of pain in Parkinson’s disease. Korean J Pain. 2020;33(1):90–6.
6. Fasano A, Daniele A, Albanese A. Treatment of motor and non-motor features of Parkinson’s disease with deep brain stimulation. Lancet Neurol. 2012;11(5):429–42.
7. Braak H, Braak E, Yilmazer D, Schultz C, de Vos R, Jansen E. Nigral and extranigral pathology in Parkinson’s disease. J Neural Transm Suppl. 1995;(46):15–31.
8. Klingelhoefer L, Reichmann H. Parkinson’s disease as a multisystem disorder. J Neural Transm. 2017;124(6):709–13.
9. Rukavina K, Leta V, Sportelli C, Buhidma Y, Duty S, Malcangio M, et al. Pain in Parkinson’s disease: New concepts in pathogenesis and treatment. Curr Opin Neurol. 2019;32(4):579–88.
10. Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, et al. Update on treatments for nonmotor symptoms of Parkinson’s disease—

an evidence-based medicine review. Mov Disord. 2019;34(2):180–98.

11. Jost WH, Buhmann C. The challenge of pain in the pharmacological management of Parkinson's disease. Expert Opin Pharmacother. 2019;20(15):1847–54.

12. Cury RG, Galhardoni R, Fonoff ET, Dos MG, Ghilardi S, Fonoff F, et al. Effects of deep brain stimulation on pain and other nonmotor symptoms in Parkinson disease. Neurology. 2014;83(16):1403–9.

13. Treede R, Rief W, Barke A, Finnerup NB, Scholz J, First MB, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain. 2018;160(1):19–27.

14. Sá KN, Moreira L, Baptista AF, Yeng LT, Teixeira MJ, Galhardoni R, et al. Prevalence of chronic pain in developing countries: Systematic review and meta-analysis. Pain Reports. 2019;4(6):1–8.

15. Defazio G, Berardelli A, Fabbrini G, Martino D, Fincati E, Fiaschi A, et al. Pain as a Nonmotor Symptom of Parkinson Disease Evidence From a Case-Control Study. Arch Neurol. 2008;65(9):1191–4.

16. Tinazzi M, Del Vesco C, Fincati E, Ottaviani S, Smania N, Moretto G, et al. Pain and motor complications in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2006;77(7):822–5.

17. Mylius V, Perez Lloret S, Cury RG, Teixeira MJ, Barbosa VR, Barbosa ER, et al. The Parkinson disease pain classification system: results from an international mechanism-based classification approach. Pain. 2021;162(4):1201–10.

18. Freynhagen R, Parada HA, Calderon-Ospina CA, Chen J, Rakhmawati Emril D, Fernández-Villacorta FJ, et al. Current understanding of the mixed pain concept: a brief narrative review. Curr Med Res Opin. 2019;35(6):1011–8.

19. Melzack R, Wall P. Pain mechanisms: a new theory. Science (80-). 1965;

20. De Andrade DC, Bendib B, Hattou M, Keravel Y, Nguyen JP, Lefaucheur JP. Neurophysiological assessment of spinal cord stimulation in failed back surgery syndrome. Pain. 2010 Sep;150(3):485–91.

21. De Ridder D, Vanneste S. Burst and tonic spinal cord stimulation: Different and common brain mechanisms. Neuromodulation. 2016;19(1):47–59.

22. Chakravarthy K, Fishman MA, Zuidema X, Hunter CW, Levy R. Mechanism of Action in Burst Spinal Cord Stimulation: Review and Recent Advances. Pain Med (United States). 2019;20(Suppl 1):S13–22.

23. Kirketeig T, Schultheis C, Zuidema X, Hunter CW, Deer T. Burst Spinal Cord Stimulation: A Clinical Review. Pain Med (United States). 2019;20(Suppl 1):S31–40.

24. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30(12):1591–601.

25. Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DLH, Bouhassira D, et al. Neuropathic pain: An updated grading system for research and clinical practice. Pain. 2016;157(8):1599–606.

26. de Andrade DC, Ferreira KASL, Nishimura CM, Yeng LT, Batista AF, de Sá K, et al. Psychometric validation of the Portuguese version of the Neuropathic Pain Symptoms Inventory. Health Qual Life Outcomes. 2011;9:107.

27. De Martino E, Fernandes AM, Galhardoni R, De Oliveira Souza C, Ciampi De Andrade D, Graven-Nielsen T. Sessions of Prolonged Continuous Theta Burst Stimulation or High-frequency 10 Hz Stimulation to Left Dorsolateral Prefrontal Cortex for 3 Days Decreased Pain Sensitivity by Modulation of the Efficacy of Conditioned Pain Modulation. J Pain. 2019;20(12):1459–69.

28. Trenkwalder C, Chaudhuri KR, Martinez-Martin P, Rascol O, Ehret R, Vališ M, et al. Prolonged-release oxycodone-naloxone for treatment of severe pain in patients with Parkinson's disease (PANDA): A double-blind, randomised, placebo-controlled trial. Lancet Neurol. 2015;14(12):1161–70.

29. Botega NJ, Bio MR, Zomignani MA, Garcia C, Pereira WA. Mood disorders among inpatients in ambulatory and validation of the anxiety and depression scale HAD. Rev Saude Publica. 1995;29(5):355–63.

30. Santos M, Cintra MACT, Monteiro AL, Santos B, Gusmão-Filho F, Andrade MV, et al. Brazilian valuation of EQ-5D-3L health states. Med Decis Mak. 2016;36(2):253–63.

31. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord. 2008;23(15):2129–70.

32. Ferreira KA, Teixeira MJ, Mendonza TR, Cleeland CS. Validation of brief pain inventory to Brazilian patients with pain. Support Care Cancer. 2011;19(4):505–11.

33. De Lima MS, Soares BGDO, Paoliello G, Vieira RM, Martins CM, Neto JIDM, et al. The Portuguese version of the Clinical Global Impression - Schizophrenia Scale: Validation study. Rev Bras Psiquiatr. 2007;29(3):246–9.

34. Rocha RDO, Teixeira MJ, Yeng LT, Cantara MG, Faria VG, Liggieri V, et al. Thoracic sympathetic block for the treatment of complex regional pain syndrome type I: A double-blind randomized controlled study. Pain. 2014;155(11):2274–81.

35. Dongyang L, Fernandes AM, da Cunha PHM, Tibes R, Sato J, Listik C, et al.

Posterior-superior insular deep transcranial magnetic stimulation alleviates peripheral neuropathic pain — A pilot double-blind, randomized cross-over study. Neurophysiol Clin. 2021;51(4):291–302.

36. Harrell Jr F. Regression Modeling Strategies With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. Cham: Springer-Verlag; 2015. 582 p.

37. Fitzmaurice G, Laird N, Ware J. Applied longitudinal analysis. 2nd ed. Hoboken, NJ: Wiley; 2012. 752 p.

38. Twisk J. Applied Longitudinal Data Analysis for Epidemiology: A Practical Guide. Second ed. Amsterdam: Cambridge University Press; 2013. 321 p.

39. Ciampi De Andrade D, Lefaucheur JP, Galhardoni R, Ferreira KSL, Brandão Paiva AR, Bor-Seng-Shu E, et al. Subthalamic deep brain stimulation modulates small fiber-dependent sensory thresholds in Parkinson's disease. Pain. 2012;153(5):1107–13.

40. Slaoui T, Mas-Gerdelat A, Ory-Magne F, Rascol O, Brefel-Courbon C. La lévodopa modifie les seuils nociceptifs chez le patient parkinsonien. Rev Neurol (Paris). 2007;163(1):66–71.

41. Cury RG, Galhardoni R, Teixeira MJ, Dos Santos Ghilardi MG, Silva V, Myczkowski ML, et al. Subthalamic deep brain stimulation modulates conscious perception of sensory function in Parkinson's disease. Pain. 2016;157(12):2758–65.

42. Kim HJ, Jeon BS, Lee JY, Paek SH, Kim DG. The benefit of subthalamic deep brain stimulation for pain in parkinson disease: A 2-year follow-up study. Neurosurgery. 2012;70(1):18–23.

43. Spielberger S, Wolf E, Kress M, Seppi K, Poewe W. The influence of deep brain

stimulation on pain perception in Parkinson's disease. Mov Disord. 2011;26(7):1367–8.

44. Li J, Mi TM, Zhu B fan, Ma JH, Han C, Li Y, et al. High-frequency repetitive transcranial magnetic stimulation over the primary motor cortex relieves musculoskeletal pain in patients with Parkinson's disease: A randomized controlled trial. Park Relat Disord. 2020 Nov 1;80:113–9.

45. Djaldetti R, Yust-Katz S, Kolianov V, Melamed E, Dabby R. The effect of duloxetine on primary pain symptoms in Parkinson disease. Clin Neuropharmacol. 2007;30(4):201–5.

46. Iwaki H, Ando R, Tada S, Nishikawa N, Tsujii T, Yamanishi Y, et al. A double-blind, randomized controlled trial of duloxetine for pain in Parkinson's disease. J Neurol Sci. 2020;414:116833.

47. Chakravarthy K V., Chaturvedi R, Agari T, Iwamuro H, Reddy R, Matsui A. Single arm prospective multicenter case series on the use of burst stimulation to improve pain and motor symptoms in Parkinson's disease. Bioelectron Med. 2020;6(1):4–11.

48. Lee MA, Walker RW, Hildreth TJ, Prentice WM. A Survey of Pain in Idiopathic Parkinson's Disease. J Pain Symptom Manage. 2006;32(5):462–9.

49. Cogiamanian F, Vergari M, Pulecchi F, Marceglia S, Priori A. Effect of spinal transcutaneous direct current stimulation on somatosensory evoked potentials in humans. Clin Neurophysiol. 2008;119(11):2636–40.

50. Guidetti M, Ferrucci R, Vergari M, Aglieco G, Naci A, Versace S, et al. Effects of Transcutaneous Spinal Direct Current Stimulation (tsDCS) in Patients With Chronic Pain: A Clinical and Neurophysiological Study. Front Neurol. 2021;12.

51. Mingyuan W, Bengt L, Robert D. F. Putative mechanisms behind effects of

spinal cord stimulation on vascular diseases. 2009;138(405):9–23.

52. Squair JW, Berney M, Castro Jimenez M, Hankov N, Demesmaeker R, Amir S, et al. Implanted System for Orthostatic Hypotension in Multiple-System Atrophy. N Engl J Med. 2022;386(14):1339–44.

53. Tang R, Martinez M, Goodman-Keiser M, Farber JP, Qin C, Foreman RD. Comparison of burst and tonic spinal cord stimulation on spinal neural processing in an animal model. Neuromodulation. 2014;17(2):143–51.

54. Linderoth B, Meyerson BA. Spinal cord stimulation: Exploration of the physiological basis of a widely used therapy. Anesthesiology. 2010;113(6):1265–7.

55. Guan Y, Wacnik PW, Yang F, Carteret AF, Chung C-Y, Meyer RA, et al. Spinal Cord Stimulation-induced Analgesia Electrical Stimulation of Dorsal Column and Dorsal Roots Attenuates Dorsal Horn Neuronal Excitability in Neuropathic Rats. Anesthesiology. 2010;113(6):1392–405.

56. Song Z, Ansah OB, Meyerson BA, Pertovaara A, Linderoth B. The rostroventromedial medulla is engaged in the effects of spinal cord stimulation in a rodent model of neuropathic pain. Neuroscience. 2013;247:134–44.

57. Moens M, Sunaert S, Mariën P, Brouns R, De Smedt A, Droogmans S, et al. Spinal cord stimulation modulates cerebral function: An fMRI study. Neuroradiology. 2012;54(12):1399–407.

58. Insausti-Delgado A, Lopez-Larraz E, Nishimura Y, Birbaumer N, Ziemann U, Ramos-Murguialday A. Quantifying the effect of trans-spinal magnetic stimulation on spinal excitability. Int IEEE/EMBS Conf Neural Eng NER. 2019;2019-March:279–82.

59. Nakagawa K, Nakazawa K. Static magnetic field stimulation applied over the

cervical spinal cord can decrease corticospinal excitability in finger muscle. Clin Neurophysiol Pract. 2018;3:49–53.

60. Liu H, Xiong D, Pang R, Deng Q, Sun N, Zheng J, et al. Effects of repetitive magnetic stimulation on motor function and GAP43 and 5-HT expression in rats with spinal cord injury. J Int Med Res. 2020;48(12).

61. Lenoir C, Jankovski A, Mouraux A. Anodal Transcutaneous Spinal Direct Current Stimulation (tsDCS) Selectively Inhibits the Synaptic Efficacy of Nociceptive Transmission at Spinal Cord Level. Neuroscience. 2018;393:150–63.

62. Murray LM, Knikou M. Repeated cathodal transspinal pulse and direct current stimulation modulate cortical and corticospinal excitability differently in healthy humans. Exp Brain Res. 2019;237(7):1841–52.

63. Murray LM, Islam MA, Knikou M. Cortical and Subcortical Contributions to Neuroplasticity after Repetitive Transspinal Stimulation in Humans. Terao Y, editor. Neural Plast. 2019;2019:4750768.

64. Saini HS, Shnoda M, Saini I, Sayre M, Tariq S. The Effects of Spinal Cord Stimulators on End Organ Perfusion: A Literature Review. Cureus. 2020;12(3):e7253.

65. Galhardoni R, Da Silva VA, García-Larrea L, Dale C, Baptista AF, Barbosa LM, et al. Insular and anterior cingulate cortex deep stimulation for central neuropathic pain disassembling the percept of pain. Neurology. 2019;92(18):E2165–75.

66. Faber J, Fonseca LM. How sample size influences research outcomes. Dental Press J Orthod. 2014;19(4):27–9.

67. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V,

et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). Clin Neurophysiol. 2020;131(2):474–528.

68. Al-Kaisy A, Baranidharan G, Sharon H, Palmisani S, Pang D, Will O, et al. Comparison of Paresthesia Mapping With Anatomic Placement in Burst Spinal Cord Stimulation: Long-Term Results of the Prospective, Multicenter, Randomized, Double-Blind, Crossover CRISP Study. Neuromodulation. 2022;25(1):85–93.

69. De Carolis G, Paroli M, Tollapi L, Doust M, Burgher AH, Yu C, et al. Prospective Evaluation Paresthesia-Independence: An Assessment of Technical Factors Related to 10 kHz Paresthesia-Free Spinal Cord Stimulation. Pain Physician. 2017;20:331–41.

70. Bannister K, Kucharczyk MW, Graven-Nielsen T, Porreca F. Introducing descending control of nociception: a measure of diffuse noxious inhibitory controls in conscious animals. Pain. 2021;162(7):1957–9.

FIGURE LEGENDS

Figure 1. Stimulation montage.

Figure 2. CONSORT study diagram.

TABLES

Table 1. Demographic profile and baseline characteristics of subjects included in the study.

Table 2. Influence of bTsMS on pain response within the first eight weeks.

Table 3. Secondary outcomes.

Table 1. Demographical profile and baseline assessment characteristics of subjects included in the study.

		Sham bTsMS (n= 13)	Active bTsMS (n= 13)
Age (years)[A]		61.4±9.2(42-79)	61.9±10.3(36-73)
Sex, n (%)	*Male*	9(69.2)	5(38,5)
Schooling, n (%)	*< 12 years*	7(53.8)	5(38.5)
	> 12 years	6(46.2)	8(61.5)
Etiology of musculoskeletal pain, n (%)	*Myofascial pain syndrome*	12(92.3)	12(92.3)
	Coat hanger headache	2(15.4)	2(15.4)
	Localized pain	4(30.8)	3(23.1)
Handedness, n (%)	*Right-handed*	12(92.3)	13(100.0)
Time since Parkinson disease ‘s diagnosis (years)[A]		9.3± 7.5(0-26)	10.9± 5.2(1-20)
Levodopa equivalent[A]		936.4±468.7(300-1905)	847.8±425.7(150-1564)

Table 1(continued). Demographical profile and baseline assessment characteristics of subjects included in the study.

Side of initial motor symptom, n (%)	*Left*	7(50.0)	7(50.0)
	Right	6(50.0)	6(50.0)
Predominant pain side, n (%)	*Bilateral*	7(53.8)	11(84.6)
	Left	3(23.1)	2(15.4)
	Right	3(23.1)	0(0.0)
Pain location, n (%)	*Neck*	5(38.5)	4(30.8)
	Shoulder	5(38.5)	6(46.1)
	Upper limb	2(15.4)	3(23.1)
	Upper back	1(7.7)	2(15.4)
	Low back	9(69.2)	10(76.9)
	Lower Limb	9(69.2)	9(69.2)

Table 1(continued). Demographical profile and baseline assessment characteristics of subjects included in the study.

Duration of pain (years)[B]		4.5±3.9(0.5-5)	5.6±5.4(1-8)
Average pain (BPI)[A]		7.0±1.3(5-10)	6.1±1.7(4-10)
New pain in the last evaluation, n (%)		1(7.7)	3(23.1)
Rehabilitation, n (%)		6(46.2)	8(61.5)
Pain catastrophizing scale[A]		26.4±14.5	27.0±9.0
HADS	*Depression subscale*	7.6±5.6	7.1±3.2
	Anxiety subscale	9.5±5.2	7.7±3.2
Motor complications in Parkinson disease, n (%)	*Motor fluctuations*	6(46.2)	6(46.2)
	Dyskinesia	5(38.5)	7(53.8)
	Gait problems	9(69.2)	10(61.5)
UPDRS part III		33.2±16.3(10-67)	43.0±16.1(14-66)

Table 1(continued). Demographical profile and baseline assessment characteristics of subjects included in the study.

Hoehn and Yahr scale, n (%)	*Unilateral*	2(15.4)	2(15.4)
	Bilateral	8(61.5)	11(84.6)
	Bilateral with balance and postural impairment	3(23.1)	0(0.0)
DBS, n (%)		3(23.1)	2(15.4)

[A] Values are presented in: mean ± SD (minimum and maximum); [B] Values are present in: medium (quartiles);

bTsMS: burst trans-spinal magnetic stimulation BPI: brief pain inventory; HADS: Hospital anxiety and depression scale; UPDRS: total unified Parkinson disease rating scale; DBS: Deep brain stimulation.

Table 3. Secondary outcomes.

		(N=26)	(N=22)
	Group	**Baseline**	**Eighth Week**
PD-PCS score	Active bTsMS	43.4±20.0(12-90)	10.0±13.8(0-42)
	Sham bTsMS	43.2±22.1(12-72)	26.2±23.1(0-63)
HADS-D*	Active bTsMS	7.1±3.2(2-12)	4.0±3.1(0-9)
	Sham bTsMS	7.6±5.6(1-21)	8.7±5.3(2-18)
HADS-A	Active bTsMS	7.7±3.2(2-12)	4.1±2.3(1-8)
	Sham bTsMS	9.5±5.2(2-20)	6.6±5.1(1-16)
EQ-5D-3L total	Active bTsMS	0.44±0.13(0.30-0.74)	0.67±0.15(0.49-0.85)
	Sham bTsMS	0.49±0.14(0.17-0.69)	0.53±0.19(0.35-0.85)
EQ-5D-3L Health Score	Active bTsMS	56.4±5.23.8(0-95)	71.9±14.5(50-99)
	Sham bTsMS	55.8±29.5(1-85)	62.9±22.7(10-95)
UPDRS part III	Active bTsMS	43.0±16.1(14-66)	36.0±8.6(22-48)
	Sham bTsMS	33.2±16.3(10-67)	38.0±17.0(10-78)
BPI Pain Intensity Index	Active bTsMS	54.8±18.3.8(27.5-90.0)	19.8±19.8(0.0-55.0)
	Sham bTsMS	57.1±12.6(35.0-77.5)	35.6±21.6(0.0-75.0)
BPI Pain Interference on daily activities	Active bTsMS	65.4±17.8(31.9-90.0)	21.3±30.0(0.0-74.3)
	Sham bTsMS	68.2±18.3(42.9-97.1)	45.3±34.3(0.0-94.3)

Values are presented in: mean ± SD (minimum and maximum); bTsMS: burst trans-spinal magnetic stimulation; PD-PCS score: Parkinson Disease Pain Classification system score; HADS-D: depression subscale of the hospital

anxiety and depression scale; HADS-A: anxiety subscale of the hospital anxiety and depression scale; EQ-5D-3L: the three-level EuroQol five-dimensional questionnaire; UPDRS part III: unified Parkinson's disease rating scale part III; BPI: Brief pain inventory; * $P<0.05$ (results obtained by two-way repeated measures ANOVA analysis between baseline and eighth week based on group-by-time interaction effect).

Table 2. Influence of bTsMS on pain response within the first eight weeks.

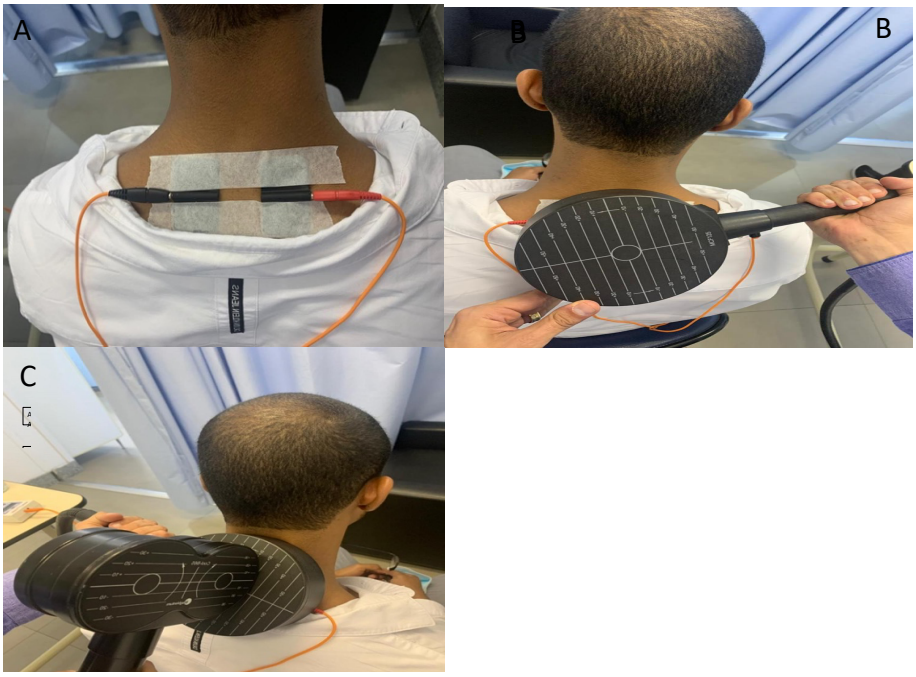
			(N=26)		
	β	**Standard Error**	**OR**	**95% CI**	**p**
Intercept	-1.338	0.5924	0.261	0.082-0.834	0.023*
Week	0.111	0.0784	1.138	0.977-1.327	0.099
Active treatment group	1.347	0.6689	3.844	1.036-14.262	0.044*

Results obtained by Generalized Estimating Equations (GEE) analysis, weeks 1-8 included as a covariate;

Pain intensity [Average NRS (numerical rating scale; 0-10)]; bTsMS: burst trans-spinal magnetic stimulation.

* P<0.05. Pain response defined as pain intensity reduction of at least 50% compared to baseline.

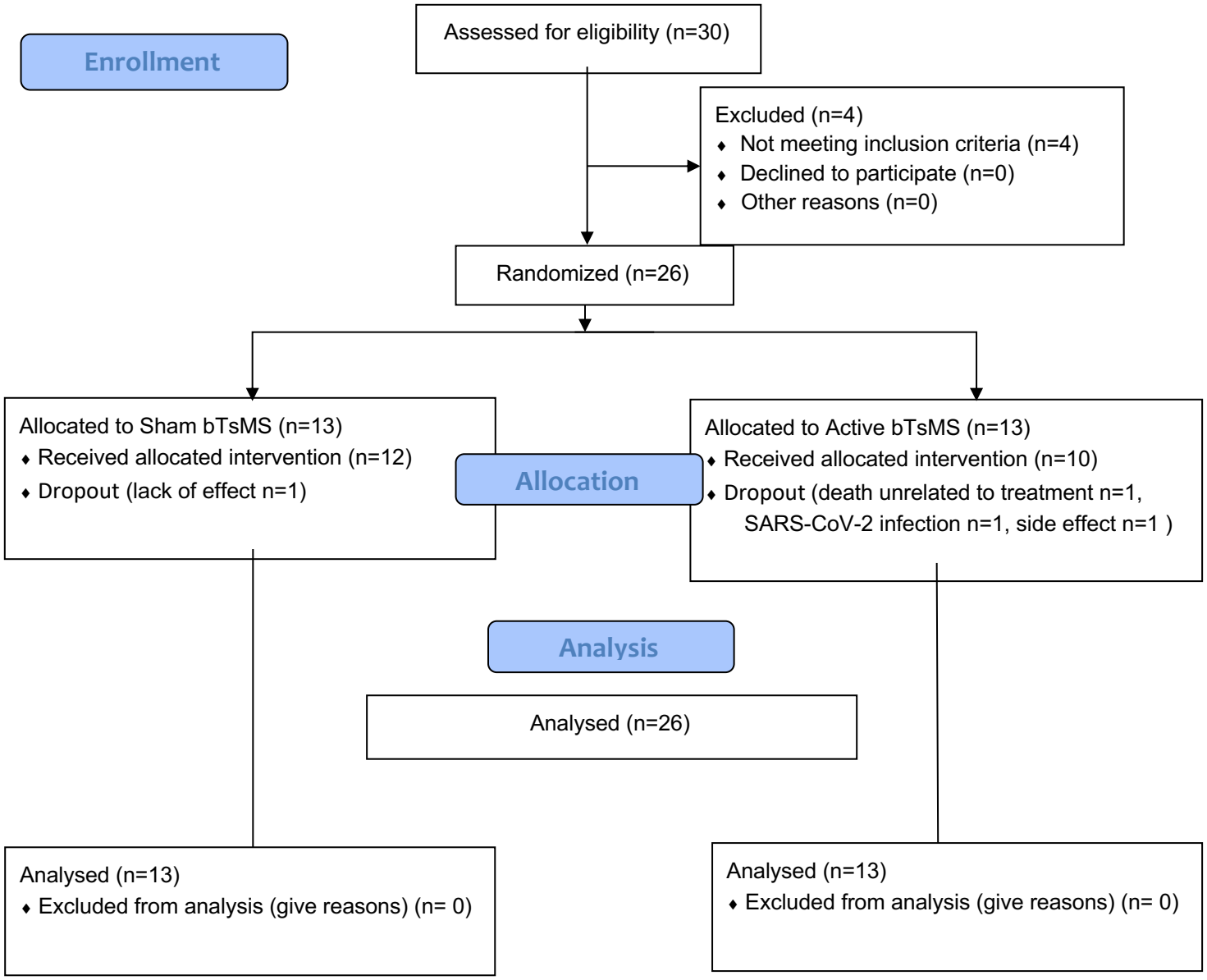
Figure 1. Stimulation montage.



A) Surface electrodes of TENS secured to the skin with adhesive tape at level of C7 in the paraspinal area. B) The circular-shaped coil placed perpendicular to spinal in midline over C7. C) The figure-eight coil was placed orthogonally to circular-shaped coil. This last image shows complete montage during all bTsMS sessions regardless of group.

TENS: Transcutaneous electrical nerve stimulation; C7: Seventh cervical vertebrae; bTsMS: Burst trans-spinal magnetic stimulation

Figure 2. CONSORT study diagram.



bTsMS: burst trans-spinal magnetic stimulation