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Effect of a 10-day transcutaneous trigeminal nerve stimulation (TNS) protocol for depression amelioration: A randomized, double blind, and sham-controlled phase II clinical trial

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ABSTRACT

Background: Major depressive disorder (MDD) is one of the leading causes of disability in the world. However, treatment options are still limited, and marked by high refractoriness rates, new approaches are needed to optimize clinical improvement. Trigeminal nerve stimulation (TNS) is an innovative neuromodulation strategy consisting on the application of an electric current over the trigeminal nerve that propagates stimuli towards brain areas involved in mood control.
Objective: We examined the effects of TNS in MDD after a 10-day experimental protocol.
Methods: This was a randomized, double blind, and sham-controlled phase II study with 24 patients with severe MDD. Patients underwent a 10-day intervention protocol and were assessed with the 17-item Hamilton Depression Rating Scale (HDRS-17) at following three observation points: baseline (T1), after 10 days (T2), and after one month of the last stimulation session (T3). Main clinical outcome analysis of variance (ANOVA) was performed.
Results: Patients in the active group presented a mean reduction of 36.15% in depressive symptoms after the stimulation protocol. There was a significant interaction between group and time regarding HDRS-17 scores ($F = 3.18$; $df = 2$; $p = 0.0456$). Post hoc analyses exhibited a statistically significant difference between active and sham group symptoms at T2 ($p = 0.040$) and T3 ($p = 0.026$), which highlights the sustained amelioration of depressive symptoms.
Conclusion: The present study found amelioration of depressive symptoms for patients undergoing a 10-day stimulation protocol of TNS, and this was sustained after one month of follow-up.

1. Background

1.1. Major depressive disorder

Major depressive disorder (MDD) is a clinical condition characterized by depressive episodes that alternate with periods of normal mood. These episodes are marked with depressed mood, anhedonia (lack of pleasure in previously pleasurable activities) and accessory symptoms like alterations in sleep, appetite, psychomotricity, besides pessimistic thoughts, and even attempts of suicide. Half of the episodes are recurrent, and in one-third of them, treatment refractoriness occurs (symptoms persist despite adequate use of antidepressants) [1].

In an epidemiological study conducted in the United States, the prevalence of MDD was 16.2%, with a mild clinical presentation in 10.4% of the cases, 38.6% moderate, 38% severe, and 12.9% very serious. Despite this, only 51.6% of the patients received specific treatment, and only 41.9% received adequate treatment according to the recommended guidelines in psychiatric practice [2]. In fact, MDD has already underscored as one of the leading causes of disability in the world, together with ischemic heart disease. In this way, MDD is a common, highly prevalent chronic psychiatric disorder with significant morbidity [3].

Current challenges in the treatment of depression, such as the issue of adherence to medication, the presence of limiting adverse effects, and the high refractoriness rates, motivate the research of new therapeutic modalities such as noninvasive neuromodulation [4,5].

1.2. Trigeminal nerve stimulation (TNS)

Trigeminal nerve stimulation (TNS) is a novel approach for the treatment of depression. Primary studies investigating the role of cranial nerve stimulation in brain function modulation concentrated on vagus nerve stimulation and its use as adjunctive treatment of drug-resistant epilepsy [6,7] and mood disorders [8,9]. However, in order to avoid possible cardiac or other vagally mediated adverse events, the following

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studies have shifted the focus to the use of TNS for the treatment of MDD, considering its direct connections to key brain regions related to mood control, such as the locus ceruleus (LC), the *raphe nuclei*, *tractus solitarius* (NTS), medullary reticular activating system (RAS), thalamic structures, limbic, and other cortical and subcortical structures [10–13]. Another crucial factor is that trigeminal nerves' branches can be easily stimulated transcutaneously.

Trigeminal nerve stimulation works through electrical stimulation with asymmetrical biphasic pulse wave adjustable from 0 to 100 mA. Usual delivery parameters are 120 Hz frequency with 250 microseconds pulse wave duration and cycles of 30 s [14].

There are still few studies that investigated TNS for the treatment of MDD [15–17]. To the best of our knowledge up to this date, there was only one double blind, sham-controlled trial of TNS for the treatment of patients with depression [18]. This scenario motivated us to perform the present study.

2. Methods

2.1. Overview

We conducted a phase II randomized, sham-controlled trial. The study was approved by the Institutional Review Board of the Faculty of Medical Sciences of Santa Casa de Sao Paulo, and all study procedures were performed in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki. Prior to the study, informed consent was obtained from all patients using procedures, and consent forms were approved by our Institutional Review Board. The experiment was carried out at our Clinical Neuromodulation Laboratory. Patient's clinical assessment and outcome scores were evaluated at baseline (T1), after 10 days of treatment (T2), and after one month of the last stimulation session (T3).

2.2. Study design

A total of 24 patients naive to neurostimulation techniques with severe MDD were included in the study. Voluntaries were recruited through local flyers, newspaper, and internet advertisements. Included participants were between 18 and 69 years old with severe MDD determined by a trained psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and by baseline depression score ≥ 19 according to the 17-item Hamilton Depression Rating Scale (HDRS-17).

Patients could be on antidepressants, benzodiazepines, and augmentation strategies with mood stabilizers or antipsychotics but had to be at a steady dose for at least four weeks before assessment and were instructed to maintain the same dose for the duration of the trial. The Mini-International Neuropsychiatric Interview was completed to assess and exclude patients with psychiatric comorbidities, and a physical examination assessed current physical health. Individuals with neurological or clinical disorders, pregnancy, or any implanted metal devices (e.g., pacemakers, metal plates, wires) were also excluded. Patients were then randomized into active or sham groups.

For sample size prediction, we adopted an alpha level of 0.05, a power of 80%, and a minimal significant reduction of three points on the HDRS-17.

2.3. Assessment

The primary outcome was the mean difference in the 17-item investigator-rated HDRS-17 at T2 and T3. Possible total scores on the HDRS-17 range from 0 (no symptoms) to 52 (most severe). Secondary efficacy measures consisted of cognitive function as assessed by the Montreal Cognitive Assessment (MoCA) and the quality of life assessed by the World Health Organization Quality of Life (WHOQOL) instrument. We analyzed data from the full intent-to-treat sample using a repeated measures analysis of variance (ANOVA) with treatment as the between-subject factor and time as the within-subject factor. The significance level was set at $p \leq 0.05$. All analyses were carried out using the statistical software Stata® 13.1 (StataCorp., College Station, Texas, USA).

2.4. Experimental protocol

For active stimulation, we adopted the external neurostimulator (Ibramed Neurodyn®) approved by our National Regulatory Agency. Stimulation parameters were based on a previous successful protocol [18]. The 10-day experimental protocol was applied over a two-week period with daily 30-min sessions (on weekdays). Stimulation was delivered with a pulse frequency of 120 Hz and 250 μs of pulse duration. We used two 25-cm^2 electrodes with saline solution-soaked sponges positioned bilaterally over the supraorbital foramen to stimulate V1 branches of the trigeminal nerve. Intensity was adjusted to maintain levels of stimulation that were clearly perceptible but not uncomfortable. Patients were evaluated after each session in search for possible adverse effects. Regarding sham protocol, the device was turned off after 60 s of stimulation. After this initial period, the referred paresthesia seems to diminish because of nerve adaptation.

2.5. Randomization and blinding

The chosen randomization strategy was the block randomization method, designed to randomize participants into groups that result in equal sample. Randomization process was performed with a randomization generator (www.randomization.com). Randomized participants as well as the main evaluator were blinded. During the stimulation sessions, participants of each group were kept in separate procedure rooms with their back to the stimulation devices that were covered. As to reinforce blinding, participants in each room did not face each other while receiving the stimulation and were asked not to interact during the procedure. The randomization list was kept in another building with an investigator not included in the assessment interviews. Blinding integrity was assessed after the protocol. Each participant was asked to guess if he was in the active or sham group and to rate the chance of correctly guessing.

3. Results

3.1. Overview

A total of 24 patients were enrolled and underwent randomization resulting in 12 patients in each group. The mean age of the active group was 39.16 (±12) and 43.8 years (±11.8) for sham group ($p = 0.27$). The active group presented 50% of female patients while the sham group was composed of 75% of female patients. The mean baseline HDRS-17 score was 24.6 (±4.5) in the active group and 23.6 (±3.4) in the sham group ($p = 0.593$). Patients reported a mean number of episodes of depression of 3.4 (±1.9) and 4.1 (±1.9) in the active and sham groups, respectively. The mean duration of the current episode was of 21.1 months (±12.6) in the active group and of 19.4 (±11.7) in the sham group. Patients had a mean refractoriness score of 1.7 (±1.5) and 2.6 (±2.1) in the active and sham groups, respectively (Table 1).

Table 1
Summary of clinical and demographical data.

Variable	Active	Sham
Age (mean ± SD)	39.16 (±12)	43.8 (±11.8)
Genre (%fem)	50	75
HDRS baseline ($p = 0.593$)	24.6 (±4.5)	23.6 (±3.4)
Depressive episodes ($p = 0.33$)	3.4 (±1.9)	4.1 (±1.9)
Mean duration of current episode ($p = 0.65$)	21.1 (±12.6)	19.4 (±11.7)
Refractoriness score ($p = 0.22$)	1.7 (±1.5)	2.6 (±2.1)

3.2. Primary outcome

The present study found amelioration of depressive symptoms for patients undergoing the experimental protocol. There was a significant interaction between group and time regarding HDRS-17 scores ($F = 3.18$; $df = 2$; $p = 0.0456$). Patients undergoing the experimental protocol presented with a mean reduction of 8.67 in depressive symptoms after the 10-day protocol (mean reduction of 36.15% according to the HDRS-17). Post hoc analyses exhibited a statistically significant difference between active and sham group symptoms after the stimulation protocol at T2 ($p = 0.040$) and after the follow-up period at T3 ($p = 0.026$), which highlights the sustained amelioration of depressive symptoms within the study follow-up period (Fig. 1).

3.3. Secondary outcomes and safety issues

We did not find statistically significant changes in cognition in comparison to a mean baseline score of 23.95 (± 3.26; $p = 0.455$) as assessed by the MoCA, nor has any change been underscored regarding quality of life as assessed by the WHOQOL.

Regarding blinding integrity, interestingly, after the stimulation protocol, every patient in active group was able to correctly guess the stimulation protocol (possible because of clinical amelioration), while only 50% of sham group were able to do so. The procedure was well-tolerated with most of the patients reporting only a mild paresthesia at stimulation site. There was no severe reported adverse effect, and only one patient in the active group dropped out of the study because of personal issues.

4. Discussion

Our results are aligned with previous published studies in the neuromodulation scenario showing a rapidly instated and sustained reduction in depressive symptoms of patients undergoing TNS protocols [15–18]. Interestingly, our results indicate that TNS was effective in a group of patients that, in mean scores, have been depressed for a considerable period of time and that have also tried different medications' approaches.

The precise mechanism by which TNS works is still in debate. The use of TNS for psychiatric disorders is based on theoretical mechanisms empirically tested. The current hypothesis beneath TNS stimulation is based on electric stimulation leading to direct modulatory effects in subcortical sites and changes in cortical excitability. Neuroimaging studies corroborate these effects, showing neuronal activity changes in certain sites of brain, such as the amygdala, insula, precentral gyrus, hippocampus, and thalamus [13].

4.1. Limitations

Albeit the exciting results, this study has several limitations such as the allowance of concomitant use of pharmacological treatment. Patients were required to be under a stable dose of psychiatric medications for the previous four weeks; however, it is possible that some of the improvement presented may have been due to medication adjustments prior to this period but this would probably occur in both active and sham groups.

Another limitation that ought to be addressed is the relatively small sample size. Therefore, our negative results regarding lack of changes in cognitive symptoms and quality of life assessments were possibly underpowered. Finally, we did not perform a long-term evaluation so the precise lasting of clinical effects is uncertain.

5. Final considerations

We found TNS to be effective and superior to sham stimulation in ameliorating depressive symptoms after a 10-day stimulation protocol with lasting effects after a one-month follow-up. However, larger samples and longer follow-up periods may aid to clarify how effective and long lasting TNS effects really are for treating depressive symptoms in clinical practice.

Disclosure

Dr. Marcelo B. Generoso reported no biomedical financial interests or potential conflicts of interest.

Dr. Ivan T. Taiar reported no biomedical financial interests or potential conflicts of interest.

Dr. Lucas P. Garrocini reported no biomedical financial interests or potential conflicts of interest.

Dr. Rafael Bernardon reported no biomedical financial interests or potential conflicts of interest.

Dr. Ricardo R. Uchida reported no biomedical financial interests or potential conflicts of interest.

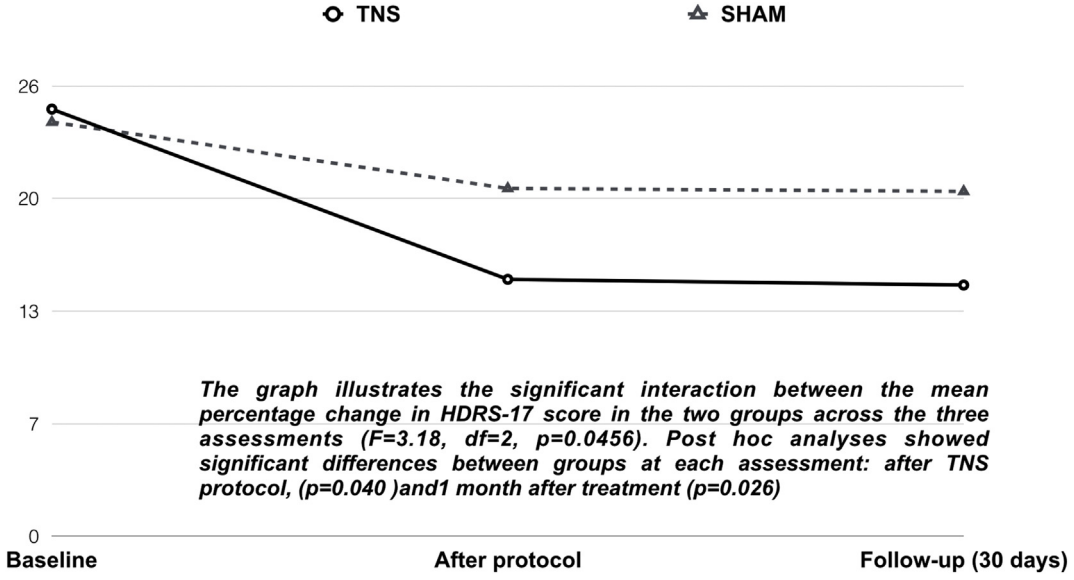

Fig. 1. Depressive symptoms changes over time.

Dr. Quirino Cordeiro reported no biomedical financial interests or potential conflicts of interest.

Dr. Pedro Shiozawa reported no biomedical financial interests or potential conflicts of interest.

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