Letter to the Editor

Transcutaneous Vagus Nerve Stimulation (taVNS) for Major Depressive Disorder: An Open Label Proof-of-Concept Trial

Dear Editor:

Despite recent advances in pharmacological treatments, Major Depressive Disorder (MDD) remains an incapacitating psychiatric condition with increasing prevalence and economic burden [1]. New therapeutical strategies such as vagus nerve stimulation (VNS) are being studied [2]. Different brain sites can be modulated by using electrical currents, which can theoretically restore balance to impaired circuits leading to clinical amelioration of symptoms. VNS involves the direct stimulation of the vagus nerve leading to further modulation of impaired brain areas related to psychiatric disorders [3,4]. Target stimulated areas include solitary tract nucleus, dorsal raphe, locus coeruleus, parabrachial area, amygdala, nucleus accumbent, hippocampus and the dorsolateral prefrontal cortex (DLPFC) [5]. Non-invasive VNS stimulation protocols have been assessed with promising results [6]. In fact, our group and others have recently proposed a hypothetically safer non-invasive approach for transcutaneously stimulating the vagus nerve in the ear, transcutaneous auricular VNS (taVNS) [7]. There are also methods for non-invasively stimulating the vagus nerve in the neck, or cervical region, called transcutaneous cervical VNS (tcVNS). We undertook this proof-of-concept study to evaluate both the safety and potential clinical efficacy of this new experimental protocol with taVNS for treating patients with MDD.

The present protocol had approval from institutional review board. Patients diagnosed with MDD according to the DSM-V criteria were recruited in an outpatient university hospital clinic. Symptom severity was assessed by the 17-item Hamilton Depression Rating Scale (HDRS). Exploratory analyses assessed depressive symptoms through the Beck Depression Inventory (BDI), anxiety symptoms through the Hamilton Anxiety Rating Scale (HAMA) and the Beck Anxiety Inventory (BAI), sleep quality through the Pittsburgh Sleep Quality Index (PSQI), and somatic symptoms through the Somatic Symptom Inventory (SSI) and the Somatoform Disorders Screening Instrument-7 days (SOMS-7). We also assessed cognitive functions with the Montreal Cognitive Assessment instrument (MoCA).

Inclusion criteria were as follows: (1) 18- to 59-year-old patients, (2) patients diagnosed with MDD following DSM-V criteria, (3) agreement to participate in the trial with written informed consent. Exclusion criteria were the following: (1) imminent need for psychiatric hospitalization, (2) any other [current or lifetime] psychiatric diagnosis, (3) neurologic or other severe diseases such as neoplastic syndromes and neurodegenerative and uncompensated chronic comorbidities, and (4) pregnancy. Clinical assessment was performed by a trained psychiatrist at baseline, at the last day of the stimulation protocol and one month after. The primary outcome was assessed by the mean difference in HDRS scores between baseline and the last day of stimulation. Participants were required to have at least four weeks without a change in psychiatric medication before the beginning of taVNS stimulation until the end of the one-month follow-up period.

All patients underwent a 10-session taVNS protocol during a two-week period. Electrical stimulation was performed using the Ibramed Neurodyn II external neurostimulator to deliver electric current through the auricular branch of the vagus nerve at 120 Hz with a pulse wave duration of 250 μs for 30 minutes per day. The intensity was set at 12 mA, which provoked a nonpainful mild paresthesia without muscle contraction for all patients. We performed the stimulation placing the electrodes bilaterally over the mastoid process area (anode to the left and cathode to the right), juxtaposed to the ear, near the tympanomastoid fissure (see Fig. 1) [8]. We used 15 cm² auto-adhesive rubber electrodes to deliver the current.

The present work was performed at the Interdisciplinary Center for Clinical Neuromodulation, Santa Casa School of Medical Sciences, São Paulo, Brazil.

References:


The main outcome and exploratory analyses were tested using ANOVA and paired t-tests. Intention-to-treat analysis was performed using the last observation carried forward method for handling with outcome missing data related to dropouts. The α level was set at 0.05. Statistical analysis was performed using the standard statistical software Stata 13.1. Sample size calculation was based on the algorithm proposed by A’Hern for single-stage trials [9]. A total of twelve patients were recruited, with a mean age of 45.9 years (sd = 9, range 32–57). Two patients were male. Mean times since first episode was of 7.5 years (sd = 7.7). There was no dropout. The mean baseline HDRS was 27.9 (sd = 4.2). All patients were under stable pharmacological protocol for at least four weeks. Treatment remained unchanged during the one-month follow-up period.

Regarding the main outcome, at the end of intervention there was a reduction of MDD symptoms from 27.9 (sd = 4.2) to 8.2 (sd = 4) (mean difference of 19.75 (sd = 4.5)) (p < 0.001) on the HDRS instrument. Considering a categorical analysis, all patients exhibited a clinical response, defined as a reduction of HDRS scores of at least 50%. Five patients presented remission of depressive symptoms defined as less than 8 points on the HDRS. Clinical response was maintained stable during the one-month follow-up period. Cognitive functioning remained stable as assessed by the MoCA (p = 0.57) (see Table 1).

All patients reported mild paresthesia underneath the electrodes during stimulation. No severe adverse effects were reported. Ten patients reported mild to moderate diurnal sleepiness after the stimulation protocol, which they attributed to the procedure. Six patients reported mild to moderate tension headaches, with no need for medication. Four patients reported mild to moderate nausea. No side effects were reported at one-month follow-up.

In the current experimental protocol, we theoretically transcutaneously accessed the auricular branch of the vagus nerve. This particular branch penetrates the mastoid canaliculus, accessing the temporal bone and emerges through the tympanomastoid fissure [7]. It then originates two branches, one that enervates the occipitofrontal muscle with the posterior auricular nerve and another branch that enervates the skin over the mastoid process and the posterior wall of the ear canal [8].

The studied 10-day taVNS protocol led to amelioration of MDD symptoms, with no severe adverse effects. Based on an easy-to-use and non-invasive technology, the present approach, if replicated in larger, more rigorous trials, may be helpful for patients with psychiatric disorders in which the neurobiology involves the vagus nerve subcortical and cortical connections, such as the amygdala, the hippocampus and the DLPFC. Our results, however, need to be analyzed under more rigorous studies that are larger and fully double blind.

Alisson P. Trevizol*, Pedro Shiozawa, Ivan Taiar, Amanda Soares, July S. Gomes, Mirna D. Barros, Bianca M. Liquidato, Quirino Cordeiro

Interdisciplinary Center for Clinical Neuromodulation, Santa Casa School of Medical Sciences, São Paulo, Brazil

* Corresponding author. Departamento de Psiquiatria, Faculdade de Ciências Médicas da Santa Casa de São Paulo, Rua Major Maraglano, 241 Vila Mariana, 04600-010 São Paulo, SP, Brazil
Tel.: +55113466 2200; fax: +551134662208
E-mail address: alisson.trevizol@hotmail.com (A.P. Trevizol)

Received 2 January 2016
Available online 10 February 2016

http://dx.doi.org/10.1016/j.brs.2016.02.001

References