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Research paper

Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: A nonrandomized controlled pilot study

Peijing Rong [a,*,1], Jun Liu [b,1], Liping Wang [c], Rupeng Liu [a], Jiliang Fang [a,b], Jingjun Zhao [a], Yufeng Zhao [d], Honghong Wang [b], Mark Vangel [e], Sharon Sun [f], Hui Ben [a], Joel Park [f], Shaoyuan Li [a], Hong Meng [a], Bing Zhu [a], Jian Kong [f,*]

[a] Institute of Acu-Mox, China Academy of Chinese Medical Sciences, Beijing 100700, China
[b] Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China
[c] Huguosi TCM Hospital, Beijing University of TCM, Beijing, 100035, China
[d] Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China
[e] Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[f] Psychiatry Department, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Background: Depression presents a significant burden to both patients and society. One treatment that has emerged is vagus nerve stimulation (VNS), an FDA-approved physical treatment for depressive disorders. However, the application of this intervention has been limited by the involvement of surgery and potential side effects. The aim of this study is to explore the effectiveness of stimulating the superficial branches of the vagus nerve as a solo treatment for MDD.

Methods: This is a nonrandomized, controlled study. The first cohort of patients (n=91) only received transcutaneous auricular VNS (taVNS) for 12 weeks. In the second cohort (n=69), patients first received 4 weeks of sham taVNS followed by 8 weeks of taVNS. All treatments were self-administered by the patients at home after they received training from the hospitals. The primary outcome measurement was the 24-item Hamilton Depression Rating Scale measured at weeks 0, 4, 8, and 12. Data analysis included a timelag analysis comparing (1) real and sham taVNS groups at week 4; (2) the real taVNS group at week 4 vs the sham taVNS group at week 8 (fourth week of real taVNS following 4 weeks of sham); and (3) the real taVNS group at week 8 vs the sham taVNS group at week 12 (eighth week of real taVNS following sham).

Results: After four weeks of treatment, MDD patients in the taVNS group showed greater improvement than patients in the sham taVNS group as indicated by Hamilton score changes as well as response and remission rates at week four. In addition, we also found that the clinical improvements continued until week 12 during taVNS.

Limitations: Patients were not randomized in this study.

Conclusions: Our results suggest that taVNS is a promising, safe, and cost-effective therapeutic method for mild and moderate MDD.

1. Introduction

Major depressive disorder (MDD) is the fourth leading cause of disability worldwide (Sackeim and Lisanby, 2001) and is projected to become the second leading cause of disability worldwide by the year 2020 (Michaud et al., 2001; Rush, 2003). Patients with MDD experience reduced quality of life in terms of psychological, physical, and social functioning, and this impairment increases with the severity of the disease (Daly et al., 2010). Antidepressant medication is considered as a first-line treatment for depression, yet up to 68% of patients stop taking antidepressants within 3 months (Gartlehner et al., 2011). Approximately 50% of patients with MDD will experience a response to first-line antidepressant therapy and one-third of patients will achieve remission with any given antidepressant, but half of these patients will experience a relapse during continuous treatment before they achieve recovery

* Correspondence to: Institute of Acu-Mox, China Academy of Chinese Medical Sciences, Beijing 100700, China (Peijing Rong); Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA (Jian Kong).
E-mail addresses: rongpj@hotmail.com (P. Rong), kongj@nmr.mgh.harvard.edu (J. Kong).
[1] Drs Peijing Rong and Jun Liu contributed equally to this work as the first authors.

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(Rush et al., 2006). Thus, despite the critical need, current treatments for MDD are far from satisfactory (Rush, 2003; Sackeim and Lisanby, 2001).

Vagus nerve stimulation (VNS) is an FDA-approved somatic treatment for treatment-resistant depression (TRD) that can produce clinically significant antidepressant effects (Daban et al., 2008; George et al., 2003; Nemeroff et al., 2006; Sackeim and Lisanby, 2001). However, the surgical risks and potentially significant side effects have limited this treatment to MDD patients who have been treated for depression but failed to respond to at least 4 prescribed medications and/or established somatic treatment options such as electroconvulsive therapy (Fitzgerald, 2013; Ventureyra, 2000).

To overcome the potential barriers of applying VNS, a non-invasive transcutaneous vagus nerve stimulation (taVNS) method has been developed. Anatomical studies suggest that the ear is the only place on the surface of the human body where there is afferent vagus nerve distribution (Henry, 2002; Peuker and Filler, 2002). According to the "bottom-up" mechanism of the CNS, the propagation of electric stimuli might follow an inverse path from peripheral nerves toward the brain stem and central structures (Shiozawa et al., 2014). Consequently, direct stimulation of the afferent nerve fibers on the ear should produce an effect similar to classic VNS in reducing depressive symptoms, but without the burden of surgical intervention (Hein et al., 2013; Rong et al., 2012). In past years, taVNS has been applied to treat disorders such as epilepsy (Rong et al., 2014; Stefan et al., 2012) and pre-diabetes (Huang et al., 2014) and has also been applied to boost associative memory in older individuals (Jacobs et al., 2015).

In a previous study (Hein et al., 2013), investigators explored the therapeutic effect of taVNS on 37 patients suffering from MDD using an add-on design (antidepressant therapy+real or sham taVNS). After two weeks of treatment, the taVNS group showed significant improvement on the Beck Depression Inventory (BDI) as compared with the sham condition. However, there was no significant difference on the Hamilton Depression Rating Scale (HAMD). Although the pilot study demonstrated that taVNS had potential as an MDD treatment, the small sample size, short length of treatment, and potential confounding of different antidepressant therapies have limited the significance of the study.

In this study, we applied a nonrandomized, controlled clinical trial to investigate the antidepressant effect of solo taVNS treatment in mild or moderate MDD patients. In the first cohort, patients received taVNS for 12 weeks to test the effectiveness of the treatment. In the second cohort, patients began with four weeks of sham taVNS followed by 8 weeks of taVNS. We hypothesize that taVNS will produce greater improvement in depression patients as compared with sham taVNS.

2. Methods

This study was registered at the Chinese Clinical Trial Registry Center (ChiCTR-TRC−11001201). The Institutional Ethics Committee of the China Academy of Chinese Medical Sciences approved this study. All clinical investigative procedures were conducted according to the principles expressed in the Declaration of Helsinki. All patients signed a consent form prior to initiation of study procedures.

Due to ethical and safety concerns, we recruited two cohorts of patients. The patients in the first cohort received only real taVNS to test the effectiveness of the treatment; the patients in the second cohort received sham taVNS only for one month before shifting to real taVNS treatment for two months (Fig. 1). The clinical outcomes (primary and secondary outcomes), inclusion and exclusion criteria, and the real and sham treatment procedures remain the same as originally registered. Some patients (n=49) were also invited to participate in an fMRI study at baseline and after 4 weeks of treatment to investigate the brain resting state functional connectivity changes before and after one month of taVNS as compared to sham taVNS. Please see the original publication for more details (Fang et al., 2015). The present study

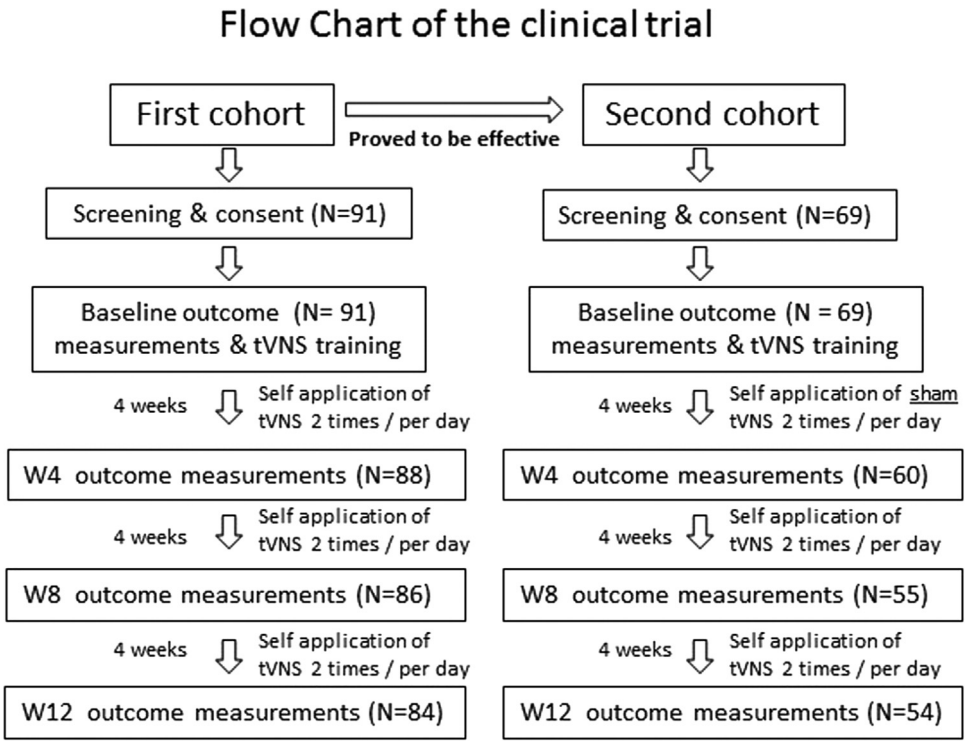

Fig. 1. The flow diagram shows detailed information regarding recruited and excluded participants.