Journal of Affective Disorders 164 (2014) 171–177

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression

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ARTICLE INFO

Article history:
Received 5 December 2013
Received in revised form
11 April 2014
Accepted 13 April 2014
Available online 21 April 2014

Keywords:
Anxiety
Depression
CES
Cranial electrotherapy stimulation

ABSTRACT

Background: Anxiety disorders are among the most prevalent mental disorders and are usually treated with medication and/or psychotherapy. When anxiety disorders are accompanied with comorbid depression, this further complicates the treatment process. Medication compliance is a common problem due to adverse side effects and new and effective treatments that have minimal side effects are needed for the treatment of anxiety and depression. This study used a randomized, double-blind, sham controlled design to examine the effectiveness of CES as a treatment for anxiety disorders and comorbid depression in a primary care setting. The study was registered at clinicaltrials.gov, NCT01533415.

Methods: One hundred and fifteen participants, age 18 years and over, with a primary diagnosis of an anxiety disorder were enrolled from February 2012 to December 2012 The Hamilton Rating Scale for Anxiety (HAM-A) and the Hamilton Depression Rating Scale$_{17}$ (HAM-D$_{17}$) were used for baseline and outcome measures at weeks one, three, and five. Response to treatment was defined as a reduction of $\geq$ 50% or more on these measures.

Results: Analysis of covariance revealed a significant difference between the active CES group and the sham CES group on anxiety ($p=0.001$, $d=0.94$) and on depression ($p=0.001$, $d=0.78$) from baseline to endpoint of study in favor of the active CES group.

Conclusions: CES significantly decreases anxiety and comorbid depression. Subjects reported no adverse events during the study.

1. Introduction

Anxiety disorders are the most common mental disorders with lifetime prevalence rates ranging from 13.6% to 28.8% (Kessler & Wang, 2008; Michael et al., 2007). According to a World Health Organization report (Andrade et al., 2000) anxiety disorders generally develop before the age of 35 in 80–90% of cases; however, differences do appear between various anxiety disorders. Research also reveals that individuals with anxiety commonly have comorbidity (Gros et al., 2013; Kessler et al., 2010) and more than three-quarters of individuals with a lifetime anxiety disorder exhibit an additional lifetime disorder (Kessler et al., 2010; Merikangas & Swanson, 2010). It has also been shown that about 50–60% of depressed individuals also meet the lifetime criteria of an anxiety disorder (Kaufman & Charney, 2000) and that anxiety disorders can be causal factors for later developing depression (Starr & Davila, 2012; Wittchen et al., 2000). Patients who have an anxiety disorder with comorbid depression have an increased number of suicide attempts compared to those without comorbid depression (Dolnak, 2006).

Medication is the standard treatment for anxiety disorders and includes selective serotonin reuptake inhibitors (SSRIs), serotonin–noreepinephrine reuptake inhibitors (SNRIs), benzodiazepines, buspirone, and tricyclic antidepressants (TCAs) (Bespalov et al., 2010). While these medications can be helpful, compliance is often compromised due to the adverse effects these medicines have on the patient including but not limited to weight gain, gastrointestinal and sexual difficulties, insomnia, and severe headaches (Lingam & Scott, 2002; Swanson et al., 2000). Due to the non-compliance issue, new and effective treatments that have minimal side effects are needed for the treatment of anxiety and depression. Cranial electrotherapy stimulation (CES) can be used as an adjunct to the pharmacological approach and psychotherapy or as an alternative therapy (Kirsch & Nichols, 2013). CES is a noninvasive brain stimulation prescriptive medical treatment (Nardone et al., 2014) that uses the application of pulsed, low amplitude electrical current to the head via electrodes placed on the earlobes; usually less than 1 mA at 0.5 Hz from either a 9 V, AAA, or AA batteries (D. Kirsch, personal communication, March 24, 2014).

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http://dx.doi.org/10.1016/j.jad.2014.04.029
0165-0327/

CES received clearance by the Food and Drug Administration (FDA) for the treatment of depression, anxiety, and insomnia in 1979 (Kirsch & Nichols, 2013). Although the mechanisms of action are not precisely known, studies have shown that CES alters the levels of various neurotransmitters in the brain (Ferdjallah et al., 1996; Liss & Liss, 1996; Shealy et al., 1998, 1989) and changes in brainwave activity (Kennerly, 2006; Electromedical Products International, Inc., 2013). According to Gilula and Kirsch (2005) it is believed that the effects of CES are mediated through the limbic system, reticular activating system (RAS), and the hypothalamus.

Many studies have explored the use and effectiveness of CES. Gilula & Kirsch (2005) indicate that at the time of their writing, there were over 160 published human research studies reporting positive results. Electromedical Products International, Inc., the manufacturer of the Alpha-Stim CES devices, maintains an active list of CES research and review articles that includes 23 randomized controlled trials; 8 open clinical trials; 5 mechanistic studies; 13 case studies; and 25 combined articles on meta-analyses, commentaries, and reviews (Electromedical Products International, 2013). Klawansky et al. (1995) reviewed 18 randomized controlled trials on the effectiveness of CES and performed a meta-analysis of the effectiveness of CES for treatment of anxiety using 14 of these studies that met the acceptance criteria for inclusion in the meta-analysis. Using effect sizes to compare outcome measures, CES was shown to be significantly more effective than sham treatment (mean Cohen's $d=0.62$ for the 14 studies).

The latest known published and registered clinical trial (clinicaltrials.gov) using CES in the treatment of anxiety was performed by Bystritsky et al. (2008). They conducted a pilot study to explore if CES was an effective treatment for patients with a DSM-IV diagnosis of GAD. Participants were excluded if they had a primary diagnosis of any other Axis I disorder other than GAD. Their study utilized a 6 week open label design with 12 participants. Diagnosis of GAD was confirmed using the Mini-International Neuropsychiatric Interview. Using the Hamilton Rating Scale for Anxiety (HAM-A) score for a baseline to week 6, a response to treatment was defined as a 50% reduction in HAM-A scores and a Clinical Global Impressions-Improvement (CGI-I) score of 1 or 2 ("much improved" or "very much improved") at the end of week 6. Medications such as SSRIs or SNRIs were permitted in the study provided they had been on a stable dose for at least 3 months and were still symptomatic. Participants taking benzodiazepines on a PRN basis were permitted to enter the study provided their frequency of use did not exceed 2 times per week. Results showed a significant decrease in HAM-A anxiety scores ($t=3.083$, $p=0.01$, $d=1.52$) from baseline to endpoint of the study. At the end of 6 weeks, 6 participants (50% of the intent-to-treat sample and 67% of those completing the study) had a 50% decrease in HAM-A scores and a CGI-I score of 1 or 2. Subjects also had significantly lower depression scores from baseline to endpoint of the study on the HAM-D_{17} ($t=3.01$, $p<0.01$, $d=0.41$). Bystritsky et al. (2008) concluded that CES appears to reduce symptoms of anxiety for individuals with a diagnosis of GAD and also for those individuals with GAD and comorbid depression. The authors recommended that future CES anxiety research include a larger sample size, utilization of sham CES treatment and requiring subjects to have a more severe anxiety level for inclusion in the study. The objective of this study was to address two of the recommendations by Bystritsky et al. (2008). We used a much larger sample size (108 versus 12 in the Bystritsky et al. (2008)) pilot study and a randomized, double-blind, sham-controlled design versus the open label pilot study design in the Bystritsky et al. (2008) study. Patients rarely present without comorbid disease in a primary care treatment setting. More often than not, patients will present with a combination of anxiety disorders such as GAD and Panic disorder, OCD, or other forms of anxiety. Anxiety disorders can be further complicated when coupled with depression.

This study examined the effects of CES on participants with any anxiety disorder. Comorbidity such as depression was included as long as the anxiety disorder was the primary diagnosis. Diagnoses for anxiety and depression were confirmed using the Structured Clinical Interview for Axis I Disorders (SCID-I). As in the Bystritsky et al. (2008) study, this study also used the HAM-A and the Hamilton Depression Rating $Scale_{17}$ (HAM-D_{17}) for baseline measurements and outcome measures (weeks 1, 3, and 5). Response to treatment was defined as a reduction of 50% or more on these measures.

2. Methods

2.1. Design

This study used a 5 week double-blind parallel group design to test CES treatment on various anxiety disorders. The study was registered at Clinicaltrials.gov NCT01533415. Participants were recruited through the clinicaltrials.gov website, advertisements placed in newspapers in three metropolitan areas of Central Virginia, and referral through local and regional general medical and psychiatric practices and Centra Health. The study was approved by the respective institutional review boards of the University and the regional health system (Centra Health). All participants signed the informed consent form prior to participating in the study. The study included 115 individuals with a primary diagnosis of an anxiety disorder.

Of concern in any clinical research is that of attrition. In an attempt to minimize the effects of attrition, each participant was carefully screened through initial phone contact where the study was described along with clarifying the inclusion and exclusion criteria for participation. If a participant matched inclusion criteria through initial phone contact, an interview was scheduled to confirm a primary diagnosis of anxiety which took place in a private practice setting. Each participant who was selected to participate in the clinical phase of the study paid a $30 entry fee which covered administrative costs for staff such as scheduling and data collection. The fee was also instituted to minimize attrition by securing a monetary commitment similar to copayment usually required in a clinical treatment setting.

2.2. Participants

Eligible participants included males and females between the ages of 18–65. Participants needed to meet DSM-IV criteria for an anxiety disorder which was confirmed using the SCID-I. Participants with comorbid depression ($n=23$) were required to have an anxiety disorder as a primary diagnosis. Participants needed to be in good medical health or, if having chronic medical conditions, these conditions needed to be stable. The participants were required to score on the lower end of mild on the HAM-A, >15. Scores on the HAM-D_{17} were allowed to range through the very severe range provided the HAM-A was the dominant score. Participants taking antidepressants were allowed to participate as long as the medication and dose were stable for at least 3 months prior to entering the study and the individual was still exhibiting symptoms of anxiety. The dose and type of medication were required to remain stable throughout the remainder of this study. The use of benzodiazepines was only acceptable provided they were prescribed PRN and were not taken more than two times per week. Potential participants were excluded if they met DSM-IV criteria for an Axis I diagnosis, other than an Anxiety Disorder, as the primary diagnosis and if the participant was