Complementary Therapies in Medicine 27 (2016) 25–29

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevierhealth.com/journals/ctim

Evaluation of the efficacy of *Withania somnifera* (Ashwagandha) root extract in patients with obsessive-compulsive disorder: A randomized double-blind placebo-controlled trial

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ARTICLE INFO

Article history:
Received 22 October 2015
Received in revised form 31 March 2016
Accepted 31 March 2016
Available online 9 April 2016

Keywords:
Randomized controlled trial
Obsessive-compulsive disorder
Withania somnifera
Ashwagandha

ABSTRACT

Background: Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder that is causally linked to dysregulation of the serotonergic system. The aim of this study is to investigate the efficacy of *Withania somnifera* (*W. somnifera*) root extract as an adjunct therapy to standard OCD treatment.
Methods: Thirty patients with a confirmed diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria participated in this randomized double-blind placebo-controlled trial and were randomly assigned to the treatment group (*W. somnifera* extract, 120 mg/day; $n = 15$) or the placebo group ($n = 15$). All patients were under treatment with Selective Serotonin Re-uptake Inhibitors (SSRIs), and were instructed to take 4 capsules of the extract or placebo per day, preferably after meals, for a period of six weeks. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) was used in order to assess the severity of OCD symptoms at baseline and at the end of the trial. Statistical analyses were performed using SPSS software and Y-BOCS values were presented as median and range (Min-Max).
Results: Comparison of the change in Y-BOCS score during the course of the trial revealed a significantly greater effect of *W. somnifera* (26 (14–40) [pre-treatment] versus 14 (4–40) [post-treatment]; change: −8 (−23 to 0)) versus placebo (18 (11–33) [pre-treatment] versus 16 (10–31) [post-treatment]; change: −2 (−4 to 0)) ($P < 0.001$). The extract was safe and no adverse event was reported during the trial.
Conclusion: W. somnifera extract may be beneficial as a safe and effective adjunct to SSRIs in the treatment of OCD.

1. Introduction

Obsessive-compulsive disorder (OCD) is a severe, chronic and often debilitating clinical disorder that is characterized by repetitive and intrusive thoughts (obsessions) which can result in distress and are thus followed by actions that can reduce this anxiety (compulsions).[1,2] Among different pathomechanisms that have been suggested for OCD, defect in the serotonergic system is known to have the most important role in the pathophysiology of this disorder.[4–6] Selective serotonin re-uptake inhibitors (SSRIs) are at the forefront of pharmacotherapy for OCD. Despite occasionally significant effects, SSRIs are usually considered to have a generally mild efficacy in patients with OCD.[7–10] Many studies have demonstrated that about 40–60% of all patients fail to respond to SSRIs, and in responsive patients symptoms are improved by 20–40%.[11–13] Moreover, augmentation therapy with other drugs, such as antipsychotics, is beneficial in only one-third of OCD patients, who did not respond to initial monotherapy with SSRIs.[14] As a result, searc for other treatments seems to be necessary.

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http://dx.doi.org/10.1016/j.ctim.2016.03.018
0965-2299/

Withania somnifera (Solanaceae), also known as Ashwagandha or Indian ginseng, is one of the most well known Ayurvedic herbal medicines which has been used as a rejuvenating and revitalizing medicinal herb for thousands of years. The roots of this plant can be used to enhance mental and physical health, especially stress-related disorders, including diabetes, hypertension, arthritis, etc.[15] It has been shown that the roots of *W. somnifera* have anxiolytic and antidepressant properties due to the presence of bioactive glycowithanolids. Moreover, the plant contains alkaloids such as withanine and somniferine that are used in nervous disorders.[15] Most importantly, it has been demonstrated in an animal study that the root extract of *W. somnifera* has a significant enhancing effect on serotonergic transmission.[16] These findings suggest that *W. somnifera* may be effective in the treatment of OCD. The safety of this plant has also been evaluated in different trials and no significant adverse effect has been reported.[17] Since there has been no prior clinical trial investigating the anti-obsessive effects of *W. somnifera*, this study was conducted to verify the efficacy of *W. somnifera* in improving the symptoms of OCD treatment.

2. Methods

2.1. Plant materials

The roots of *W. somnifera* were collected from Saravan (1165 m height), "Sistan va Baluchestan" province, Iran, in August 2013. A voucher specimen (No. 12549) was deposited at the Herbarium of the School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran. The roots were dried and grounded by an electric mill. The powdered roots (2 kg) were subjected to percolation with 70% ethanol (temperature: 45–50 °C) in order to obtain a whole crude root extract. Afterwards, the extract was evaporated under reduced pressure and then freeze dried to fine powder (120 g). Capsules (250 mg) were filled with a mixture of powdered extract and lactose (as excipient), for the treatment group. Each capsule contained 30 mg of the extract. Identical capsules were filled with lactose for the placebo group. All capsules were prepared in the industrial pharmacy lab at the Faculty of Pharmacy, Mashhad University of Medical Sciences (Mashhad, Iran), and packed in label-free bottles.

2.2. Study design and population

This study was designed as a randomized double-blind placebo-controlled trial, and was conducted between March 2015 and September 2015. The study protocol was approved by the Ethics Committee of the Mashhad University of Medical sciences. All procedures in this study were in accordance with the ethical principles established by the Declaration of Helsinki. The clinical trial protocol has been registered under the Iranian Registry of Clinical Trials (IRCT) ID: IRCT2015070523079N1 (available at: www.IRCT.ir).

Thirty patients who met the inclusion criteria entered this study. Inclusion criteria for this study were diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), and treatment with SSRI drugs with adequate dose and duration. Exclusion criteria for this study were pregnancy and lactation, comorbidity with other acute psychological disorders, drug abuse, liver and renal disorders and use of other drugs that have an effect on OCD (e.g. lithium, gabapentin and buspirone).

Eligible participants were randomly assigned to the treatment group or the placebo group using a random number Table (15 patients in each group) (Fig. 1). Randomization was carried out by a pharmacist and patients were divided into group A (treatment group) and group B (placebo group). Patients and caregivers were unaware of the allocated intervention. Identical capsules and bottles were used for both groups. Drug dispensation was based on the allocated group. Therefor, patients and caregivers were blind to the treatment.

After the initial assessment, all patients were instructed to take 4 capsules a day. To avoid possible gastrointestinal side effects, participants were instructed to start their treatment by taking one capsule a day and increasing by one capsule, every four days. Patients were also advised to take the capsules separately, preferably after meals. The medication was tapered down in the same manner, by the end of 6 weeks.

2.3. Clinical parameters

The severity of OCD symptoms was assessed in all patients using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) symptom checklist. The checklist was completed for each patient at baseline and after 6 weeks, and the data was gathered by trained interviewers.

Y-BOCS is the most widely used index for measuring the frequency and severity of symptoms in OCD patients. It is a 10-item scale with the score range of zero (no symptoms) to 40 (extreme symptoms), which provides the necessary information with respect to the time spent, resistance, distress, interference, and degree of control over all obsessions and compulsions.

2.4. Statistical analysis

Data analysis was carried out using SPSS software (version 16.0). Kruskal-Wallis and Mann-Whitney *U* tests were used to compare the changes in Y-BOCS scores between the study groups.[18] Significance of the results were also checked using the intention-to-treat method with a last observation carried forward (LOCF) approach.

3. Results

3.1. Demographic characteristics

Thirty patients were enrolled in this randomized, double-blind and placebo-controlled trial. Patients were randomly divided into treatment and placebo groups (15 patients in each group). Demographic properties, comorbid disorders, drug history and baseline Y-BOCS scores are presented in Table 1. Also, patients were monitored for likely and common adverse effects, including gastrointestinal upset, diarrhea and vomiting, but no side-effect was reported.

3.2. Comparison of the severity of OCD symptoms between treatment and placebo groups

The Y-BOCS scores were evaluated in the treatment and placebo groups at baseline and after six weeks of treatment. At baseline, the median of the Y-BOCS score was 26 (14–40) in the treatment group and 18 (11–33) in the placebo group. At the end of the trial, the median of Y-BOCS score in treatment and placebo groups were 14 (4–40) and 16 (10–31), respectively. The change of Y-BOCS score between baseline and sixth week of the study was compared in both groups. The results demonstrated that the Y-BOCS score was reduced by 8 units in the treatment group, whereas the scores were reduced by only 2 units in the placebo group. These findings demonstrate that the reduction of Y-BOCS score was significantly higher in the treatment group, compared to the placebo group ($P < 0.001$) (Table 2). The results remained significant when analyzed with LOCF intention-to-treat approach (between group difference P value = 0.004).