

Original Research Article

Effect of Wuling capsule on patients with generalized anxiety disorder

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Abstract

Purpose: To investigate the effectiveness of Wuling capsule for the treatment of patients diagnosed with generalized anxiety disorder (GAD).

Methods: Patients with generalized anxiety disorder (GAD) admitted in Affiliated Hospital of Huanghe Science and Technology College, Zhengzhou, China were treated with the Chinese traditional patent medicine, Wuling capsule. A self-control study was conducted before and after treatment. Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD), and Global Rating Scale (CGI-SI) were used to evaluate the symptoms of anxiety and depression suffered by GAD patients before and after treatment. Inflammatory factors (IL-6, IL-8, and IFN- γ), superoxide dismutase (SOD), γ -aminobutyric acid (GABA), and glutamic acid (Glu) levels were assessed in the peripheral blood of patients using ELISA before and after treatment.

Results: A total of 58 patients with GAD completed 8 weeks of fixed-dose Wuling capsule treatment. After treatment, total scores on the HAMA scale, HAMD scale, and CGI scale significantly improved compared with baseline, and the differences before and after treatment were statistically significant ($p < 0.01$). The levels of inflammatory factors (IL-6, IL-8, and IFN- γ) in the peripheral blood of patients decreased significantly ($p < 0.05$). SOD and GABA/Glu increased after treatment ($p < 0.05$). Nine patients (15.5 %) had mild reactions, but no patients withdrew from the study as result of adverse reactions.

Conclusion: The Chinese traditional patent medicine, Wuling capsule, is effective in the treatment of GAD patients with high safety. Future studies will need to explore the specific biological pathways and physiological processes that are involved in the treatment of GAD using Wuling capsule.

Keywords: Generalized anxiety disorder, Wuling capsule, Anxiety, Depression

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INTRODUCTION

Generalized anxiety disorder (GAD) is a common mental disorder with a worldwide prevalence of 5.7 % [1]. The clinical symptoms manifested by patients with GAD include continuous and

significant nervousness, accompanied by autonomic nervous function excitation, and excessive vigilance which makes it the most common anxiety disorder clinically [2]. Patients with GAD mostly present with a chronic course of disease and anxiety symptoms which cause

significant damage to patients' social functions [1].

The main ingredient of Wuling capsule is Wuling fungus powder, which has been shown to have a therapeutic effect on patients with depression and insomnia [3]. Literature has reported that a variety of Chinese traditional patent medicines are effective in managing anxiety [4]. Wuling capsules have been reported to be effective in treating anxiety symptoms such as insomnia, forgetfulness, palpitation, fatigue, and weakness [5]. This study further investigates the changes in anxiety and depression symptoms in GAD patients before and after Wuling capsule treatment, and the efficacy and safety of Wuling capsule in GAD patients.

METHODS

Patients

From July 2021 to July 2022, 68 patients with generalized anxiety disorder were admitted to the outpatient Department of the Affiliated Hospital of Yellow River University of Science and Technology. Patients were fully informed of the use of Chinese traditional patent medicine (Wuling capsule). This study was approved by the Ethics Committee of Huanghe Science & Technology College (approval no. HH202105004), and also complied with international guidelines on human studies.

Inclusion criteria

Patients that met the diagnostic criteria of ICD-10 generalized anxiety disorder, with a total score on HAMA scale of anxiety symptoms ≥ 14 points, and aged 18 – 65 years were included in the study.

Exclusion criteria

Patients with a history of epilepsy, traumatic brain injury, liver failure, renal failure, or any other disease, a history of schizophrenia, mania, or other mental diseases were excluded from the study. Other patients suffering from autoimmune diseases, or suffering from allergies, infectious diseases, a history of substance abuse, and Patients with a history of suicide were also excluded from the study.

Treatment

Patients received a fixed dose of Wuling capsules, and the therapeutic dose was 3

capsules taken orally three times daily. Treatment was administered without interfering with doctor's medication plan.

Evaluation of clinical parameters/indices

Clinical data including age, sex, onset age, education level, past course of disease, number of recurrences, and family history were collected. The Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD), and CGI-SI were used to evaluate the anxiety and depressive symptoms, and their overall severity in GAD patients [6]. The above scales were evaluated before treatment (baseline), and at 2, 4, 6, and 8 weeks after treatment.

Determination of inflammatory and oxidative factors

Eight milliliters of peripheral blood was collected from each patient before and after treatment, and serum was collected after static centrifugation. The levels of IL-6, IL-8, IFN- γ , SOD, GABA, and Glu were determined using enzyme-linked immunosorbent assay (ELISA) kit by following manufacturer's protocol.

Statistical analysis

Stata 12.0 was used for statistical analysis. Paired *t*-test was used to evaluate the scores of HAMA, HAMD, and other anxiety and depression scores before and after treatment. Patients' age, sex, education level, course of disease, and age of onset were analyzed descriptively. Grouped *t*-test was used for the analysis of measurement data while non-parametric statistics (Chi-square test or rank-sum test) was used for the analysis of count data. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics

A total of 68 GAD patients participated in the study, of which 68 (100 %) completed the Wuling capsule treatment for 4 weeks, 64 (94.1 %) for 6 weeks, and 58 (85.3 %) for 8 weeks. The demographic data and clinical characteristics of the enrolled patients who completed the study and patients who were lost to follow-up is shown in Table 1. There were no significant differences in gender, age, course of disease, family history, marital status, and educational level between the two groups ($p > 0.05$).

Table 1: General demographic data of GAD patients

Feature	All patients (n= 68)	Completely treated patient (n=58)	Lost patient (n=10)	P-value
Gender (Male/Female)	38/30	31/27	7/3	0.174
Age (years)	44.4±12.1	44.3±12.1	45.2±12.2	0.833
Duration (median)	1.1 years	1.1 years	1.2 years	0.897
Inducement time	39 cases	34 cases	5 cases	0.613
Family history	14 cases	13 cases	1 case	0.362
Marital Status (Married/other)	50/18	44/14	6/4	0.481
Years of education	7.8±5.3	7.8±5.2	7.9±5.4	0.854

Table 2: Comparison of clinical symptoms of GAD patients before and after treatment

Time point	HAMA total score	HAMD total score	CGI total score
Baseline	19.6±3.7	20.2±4.0	4.9±1.0
Week 2	13.2±4.7**	13.8±4.2**	3.8±0.9**
Week 4	8.6±4.8**	9.2±4.4**	2.7±0.9**
Week 6	6.5±4.3**	7.5±4.7**	2.1±1.0**
Week 8	4.8±3.3**	5.5±3.5**	1.7±0.8**

**P < 0.01, compared with baseline

Table 3: SOD activities and GABA/Glu before and after 8 weeks of treatment with Wulin capsule capsules (mean ± SD)

Parameter	Before treatment	After treatment	T	P-value
SOD concentration (IU/mL)	28.45±10.46	35.78±13.57	3.258	0.001
GABA/Glu	70.34±30.46	98.78±45.57	3.951	0.000

Symptoms before and after treatment

The total scores on HAMA scale, HAMD scale, and CGI-SI scale in GAD patients who completed the 8-week study were compared before and after treatment. Results showed that there were significant differences in anxiety symptom scale, depression symptom scale, and overall rating scale in GAD patients before and after treatment ($p < 0.01$), as shown in Table 2.

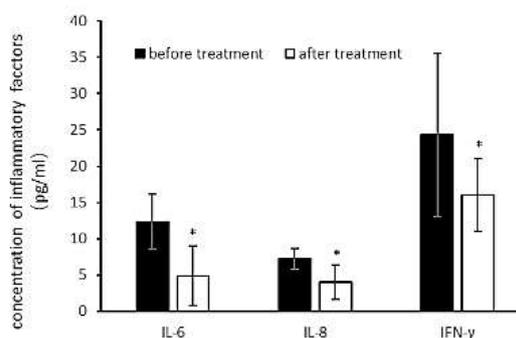
Inflammatory factors and oxidative parameters in peripheral blood

The IL-6, IL-8, and IFN- γ levels in the peripheral blood before and after treatment in patients who completed the 8-week study were compared. The levels of inflammatory factors were all significantly reduced after 8 weeks of treatment ($p < 0.05$) as shown in Figure 1. The SOD level and GABA/Glu ratio were significantly increased after treatment ($p < 0.05$) as shown in Table 3.

Adverse reactions in GAD patients

A total of 9 cases of adverse reactions were reported during the treatment in patients who completed the 8 weeks of Wuling capsules therapy. They included 3 cases of nausea, 2 cases of blurred vision, 2 cases of dry mouth, 1 case of constipation, and 1 case of dizziness. The total incidence of adverse reactions was

15.5 %, and none of the patients withdrew from the study because of the above adverse reactions.

**Figure 1:** Changes in concentration of inflammatory factors in peripheral blood of patients with generalized anxiety disorder before and after 8 weeks of treatment with Wuling capsules. *P < 0.05

DISCUSSION

Wuling capsule is a traditional Chinese medicine preparation with a single component, which is fermented by modern biotechnology from the Wuling fungus in Chinese traditional medicine [5]. Wuling fungus is the sclerotia of fungus *Xylaria nigripes* (Klotzsch) Cooke. Modern pharmacological research makes it clear that Wuling fungus contains a variety of amino acids, sterols, polysaccharides, adenosine, trace

elements, vitamins, and other components, which improve brain tissues, aid neurotransmitter permeability, and improves the patient's neuronal physiological function, thereby exhibiting an antidepressant effect resulting in calmness and sleep.

Some studies have isolated the monomer Acortatarins A and its isomers of pyrrole ring alkaloids by analyzing the chemical components of 95 % ethanol extract of Ulinum spirone powder, which has a similar structure to the clinical anti-anxiety drug buspirone [7]. Clinically, Wuling capsule is widely used in psychosomatic diseases, anxiety, depression, and other related disorders in Chinese general hospitals [3,5]. In 2021, the Clinical Practice Guideline of Integrated Traditional Chinese and Western Medicine for generalized anxiety disorder was compiled by The Chinese Association of Integrated Traditional Chinese and Western Medicine, and Wuling capsule was listed as the first-line recommended drug for the treatment of GAD [8]. There have been many studies on the treatment of depression with Wuling capsules in the past [3,5,9]. This study also showed that the symptoms of anxiety and depression and the overall condition of patients with GAD improved after Wuling capsule treatment, suggesting that Wuling capsule has a good effect on patients with GAD.

Basic studies have shown that Wuling powder increases the content of excitatory neurotransmitter glutamate and inhibitory neurotransmitter γ -aminobutyric acid (GABA), enhances the activity of glutamate decarboxylase (GAD), and improves the binding of GABA receptors in mice brains [10]. Thus, Wuling capsule improves anxiety and depression symptoms and sleep disorders through the neurotransmitters and receptors. Studies have also shown that Wuling capsule improves the abnormal release of neurotransmitters, reduces inflammatory response and oxidative stress damage, and repairs DNA damage, as well as other targets in order to reduce depression and anxiety symptoms [11]. Studies have found that conventional drugs and physical therapy sometimes don't achieve desired treatment for some patients with GAD [12-14]. For example, based on conventional drugs and physical therapy, TCM therapy does not only effectively improve the treatment of their psychological disorders, but it also reduces the severity of their physical symptoms [15,16].

This study showed that Wuling capsule use in GAD significantly decreased inflammatory factors

(IL-6, IL-8, and IFN- γ), and increased superoxide dismutase (SOD) levels in blood. The ratio of GABA to Glu was also significantly increased. Moreover, after treatment, GAD patients had fewer adverse reactions, and the degree of adverse events is relatively mild. No patient withdrew from the study because of adverse reactions, and the results showed that Wuling capsule has a good safety profile. A systematic study on patients using Wuling capsules in real-life situation using the centralized monitoring method in hospitals, also showed that the incidence of adverse reactions to Wuling capsules was rare [17]. Chinese traditional patent medicine treatment reduces patients' stigma and improves patients' compliance. Clinically, the Wuling capsule is easy to use. It is taken orally, 3 times per day. It is used alone as a single therapeutic drug [5] or combined with other Chinese and Western drugs [15,18].

Limitations of this study

This study has the following limitations: First, the sample size of the study was small, and the results may not be fully extended to efficacy in clinical practice. Secondly, this study was designed as a self-controlled study, and a control group will have to be set up for a randomized controlled study in the future, to study the efficacy of Wuling capsule compared with other anti-anxiety drugs in a more comprehensive way. In addition, only outpatients were included in the study, and the duration of drug treatment was only 8 weeks.

CONCLUSION

Wuling capsules significantly ameliorate anxiety and depression symptoms in GAD patients. Its high degree of safety may explain why it is a treatment of choice as a Chinese traditional patent medicine for GAD patients. Future studies will be required to determine its efficacy and safety of in-patients over the long-term.

DECLARATIONS

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Ethical approval

This study was approved by the Ethics Committee of Huanghe Science and Technology College, Zhengzhou, China (approval no. HH202105004),

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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