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Original article

Efficacy of Zhengtian Pill for migraine prophylaxis: A randomized, multicenter, double-blind, placebo-controlled, parallel-group study

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Abstract

Introduction: Migraine is a common neurological disorder characterized by recurrent headache attacks. Migraine treatment involves acute and prophylactic therapy. The objective of this study is to evaluate the efficacy and safety of Zhengtian Pill for migraine prophylaxis.
Methods: A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was carried out to compare the efficacy and safety of Zhengtian Pill versus placebo. A total of 247 subjects were enrolled in this study and 219 were randomized in a 1:1 ratio of Zhengtian Pill to placebo groups. After a four-week baseline period, subjects were administered Zhengtian Pill or placebo orally at a dose of 6 g, three times daily for 12 weeks. Changes from baseline in the frequency of migraine attacks, the number of days with migraine, migraine attack duration, and the number of days of acute migraine medication per four weeks in the intent-to-treat (ITT) and per-protocol (PP) populations were analyzed. The safety of Zhengtian Pill versus placebo was evaluated in the safety-evaluable population.
Results: After 12 weeks of treatment, Zhengtian Pill significantly reduced the frequency of migraine attacks, the number of days with migraine, migraine attack duration, and the number of days of acute migraine medication per four weeks in the ITT and PP populations compared with placebo. The proportion of patients experiencing any adverse event was similar between both treatment groups. Adverse events caused by Zhengtian Pill were generally mild.
Conclusions: Our results demonstrate that Zhengtian Pill can be considered as an effective and safe Chinese patent medicine for migraine prophylaxis.

Keywords: Zhengtian Pill; Migraine prophylaxis; Clinical efficacy; Safety; Randomized controlled trial; Chinese herbal medicine

Introduction

Migraine is a common neurological disorder characterized by recurrent headache attacks, which is rated by the World Health Organization (WHO) as one of the most disabling chronic disorders [1]. Several epidemiological studies have revealed that the prevalence rate of migraine is 12–14% in women and 6–8% in men [2–4]. Most migraine sufferersrequire pharmacological

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treatment due to the poor quality of life caused by migraine headache attacks [5,6]. Migraine treatment involves acute and prophylactic therapy. Acute therapy aims to stop or prevent the progression of migraine headaches or reverse migraine headaches that have started; while the aim of prophylactic therapy is to reduce the frequency and severity of migraine attacks as well as make acute attacks more responsive to acute therapy [7]. Currently, a number of western drugs have been used in clinic for the prophylactic treatment of migraine [8,9]. Although these medications have been effective in migraine prophylaxis, clinical practice has shown that the side effects of these drugs can be severe and may lead to further complications, thus limiting their use in migraine patients [10,11].

In recent years, some approaches of complementary and alternative medicine, including acupuncture and massage, have been shown to have clinical benefits for alleviating migraine headaches [12–15]. For example, randomized clinical studies demonstrate that acupuncture can effectively reduce the days with migraine and the frequency of acute medication use, especially for migraine prophylaxis [13,14]. For Chinese patent medicines (CPMs), however, few prospective, randomized, placebo-controlled clinical trials have been conducted to systematically assess their efficacy and safety in preventing migraine attacks.

Zhengtian Pill, a CPM approved by the State Food and Drug Administration (SFDA) of China in 1987, has been used in clinical practice for more than 20 years in China to stimulate blood circulation, dredge collateral, alleviate pain, and calm the liver. Although some researchers have reported that Zhengtian Pill could effectively prevent the onset of migraine attacks [16], a large-scale, randomized, prospective clinical study is still needed to fully evaluate the benefits of Zhengtian Pill for migraine prophylaxis. Therefore, according to Guidelines for Controlled Trials of Drugs in Migraine (second edition) [17], a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was performed to objectively and accurately assess the clinical efficacy and safety of Zhengtian Pill as a prophylactic therapy of migraine.

Subjects and methods

Study design

A multicenter, central randomized, double-blind, placebo-controlled, parallel-group clinical trial was conducted in this study. A total number of 247 migraine patients were enrolled by the Department of Neurology of nine clinical trial centers from April 2006 to December 2009. Randomization was designed and managed by the Clinical Medical Institute of the Chinese Medicine Academy of Science. The patients who met the inclusion criteria were randomly assigned into the experimental group and control group in a 1:1 ratio using a computer-generated stochastic system. The randomization was performed with small blocks (10 patients per block) considering extended period of recruitment and variation of patient selection with time. The patients and investigators were blinded to the group assignment. The experimental group was treated with Zhengtian Pill and the control group with placebo. Both groups accepted regular management and were permitted to use the necessary medications during migraine acute attacks.

Eligible patients were monitored during a baseline period of four weeks, during which the headache characteristics were recorded as baseline data. In this period, any use of migraine preventive medications was prohibited. After the baseline period, a 12-week treatment period and four-week follow-up period were carried out. Patients were requested to keep a headache diary throughout the whole study period, from which investigators were able to extract detailed information of migraine attacks including migraine days, frequency, duration, and intensity as well as use of acute medication during the study period. The outcome measures were evaluated at 4, 8, and 12 weeks, and during the follow-up period. The flow diagram of this study is shown in Fig. 1.

This clinical trial complied with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of all participating institutions. All participants signed an informed consent before enrollment.

Subjects

A total of 247 migraine patients were recruited by the Department of Neurology of nine clinical trial centers from April 2006 to December 2009 (Table 1). The diagnostic criteria for this clinical trial were as follows: (1) diagnostic criteria in western medicine: migraine with a typical aura or without an aura as defined by the International Classification of Headache Disorders II (ICHD-II) published in 2004 by the International Headache Society [18]; (2) diagnostic criteria in Traditional Chinese Medicine (TCM): recurrent headache with standard “Liver Wind and Blood Stasis” syndromes including headache in the left or right of head with repeated fierce attacks and long duration (several hours to days), dark red or dark purple tongue, wiry pulse, nausea, vomiting, dizziness, and blurred vision, which are defined according to diagnostic guidelines issued by the State Administration of TCM of China in 1997 [19].

The inclusion criteria were: (1) age between 18 and 50 years old (2) diagnosed as migraine with or without aura according to ICHD-II; (3) diagnosed as standard “Liver Wind and Blood Stasis” syndromes in TCM; (4) age of first onset < 50 years; (5) a history of migraine ≥ 1 year; (6) with use of analgesics < 10 times per 4 weeks; (7) with ≥ 2 and ≤ 6 times of migraine attacks per 4 weeks in the recent 12 weeks; (8) voluntary participation in this study with informed consent.

The exclusion criteria were: (1) age < 18 or >50 years; (2) a history of migraine < 1 year; (3) age of first onset ≥ 50 years; (4) with use of analgesics ≥ 10 times per 4 weeks; (5) with < 2 or >6 times of migraine attacks per 4 weeks in the recent 12 weeks; (6) previous use of Zhengtian Pill as a symptomatic or prophylactic treatment for migraine; (7) previous allergy or adverse reaction to components of Zhengtian Pill; (8) having primary disease of liver, kidney, hematopoietic system, cardiovascular system, or cerebrovascular system; (9) having headaches caused by hypertension or other chronic diseases; (10) with psychiatric