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The beneficial effects of the herbal medicine Di-huang-yin-zi (DHYZ) on patients with ischemic stroke: A Randomized, Placebo controlled clinical study

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ABSTRACT

Objectives: This study aimed to investigate the safety and therapeutic efficacy of herbal drug, Di Huang Yin Zi (DHYZ), in patients affected by ischemic stroke.
Methods: In this double blind, placebo-controlled study, a total of 100 patients with recent (less than 30 days) ischemic stroke were randomized to receive DHYZ or placebo for 12 weeks. Both groups also received rehabilitation therapy during the study period. As there were 13 dropouts, a total of 45 patients on DHYZ and 42 on placebo were available for analysis. The Fugl-Meyer Assessment (FMA) and Barthel index (BI) were assessed before treatment and at 4-week intervals.
Results: We observed that the FMA score and BI were increased, in both groups at week 4, 8 and 12 compared with the baseline. Furthermore, significantly better FMA score was observed in patients treated with DHYZ at week 8 and 12 (both $P<0.05$). BI was significantly higher in DHYZ group than in placebo group at weeks 12 ($P<0.05$). At week 12, the 95% Confidence Intervals (CI) of mean difference of FMA and BI also indicated that the differences between two groups were statistically significant. Compared to placebo, DHYZ produced significantly greater improvement in FMA grade at week 12 (44.4% versus 23.8%, $\chi^2=4.09$, $P<0.05$).
Conclusions: DHYZ showed good efficacy, safety and tolerability in patients affected by ischemic stroke. We conclude that DHYZ may be a useful therapeutic option in patients with ischemic stroke.

Contents

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1. Introduction

Stroke is the major cause of disability worldwide, and the high incidence of post-stroke disability brings a heavy burden to patients and their caregivers.[1] This problem might be aggravated greatly in the next two decades due to the aging of population,[2] especially in the developing countries.

Rehabilitation therapy may prevent sequelae or improve functional status after stroke,[3] so patients with stroke are often transferred for rehabilitation when clinically stable. But still approximately 50% of the stroke patients need long-term care even they receive regular rehabilitation therapy.[4] Many patients are dissatisfied with the poor recovery and seek for alternative therapy to improve the physical functions[5] in recent years.

Alternative therapies, including herbal medicine, acupuncture/acupressure, and moxibustion[6] are used by 42–80% of stroke patients in China.[7,8] The chronic symptoms following a stroke such as spasticity, changed muscle tone, motor neuron excitability, and ankle plantar flexor spasticity can be alleviated after acupuncture treatment.[9–13] In Japan, herbal remedies have also been used for post-stroke patients with cold sensation and numbness.[14] However, most alternative medications in stroke treatment are of unproven benefit.[15] For example, neuroAid (MLC601), a traditional Chinese medication was shown to induce neurogenesis and stimulate the development of axonal and dendritic network in an in vitro model.[16] However, a multicenter, double-blind, placebo-controlled experiment with a randomized sample of 1100 patients with ischemic stroke has statistically shown that MLC601 no better than placebo.[17] More experiments are needed to be done to better define the role of an alternative therapy in the treatment of post-stroke patients.

Di-Huang-Yin-Zi (DHYZ) is a traditional Chinese decoction that has been used for neurological disorders since Song Dynasty (approximately 900 years ago). Previous clinical experiment has shown that DHYZ significantly improve neurological function in spinal-cord-injured patients compared to placebo,[18] and thus it may be beneficial for post-stroke rehabilitation. However, there are no reported studies of its use in post-stroke treatment. This double-blind, randomized, placebo-controlled clinical study presented here investigated the efficacy and safety of DHYZ on the recovery of ischemic stroke.

2. Patients and methods

2.1. Study setting

This double-blind, placebo-controlled clinical trial was conducted at the Chang-Guo Hospital of Shandong province, China, between September 2010 and August 2013. The study protocol was approved by the Medical Ethical Committee of Chang-Guo Hospital in conformity with the Declaration of Helsinki and its subsequent amendment.

A total of 100 patients with a recent ischemic stroke were recruited to the study (Fig. 1), and the treatment period lasted 12 weeks. All participants signed an informed consent document before entering the study. Each patient was evaluated by a neurologist specialized in clinical and rehabilitation assessment.

Inclusion criteria for this study were: age between 40 and 72 years, a recent (<30 days) ischemic stroke in anterior cerebral circulation. In addition, CT scan or MRI was applied to confirm diagnosis of ischemic stroke and exclude hemorrhagic stroke.

Exclusion criteria: infarction of the basilar artery system, treatment with thrombolytic, ischemic stroke combined with hemorrhage, a Mini-Mental State Examination score <23, seizure, history of previous stroke, severe aphasia, Severe dysphagia, pneumonia, urinary tract infections, atrial fibrillation, deep vein thrombosis.

2.2. Preparation of DHYZ and placebo

DHYZ is a combination of 13 herbal drugs. The quality of the constituent herbs was in accordance with the standards set out in the Pharmacopoeia of the People's Republic of China, 2000 edition.[19]

The content of known chemical constituents in a tablet of DHYZ derived from 3 g crude herbal mixture was evaluated by high-performance liquid chromatography with electrochemical detection (Table 1). The shelf life of DHYZ is 1 year. The placebo and DHYZ were prepared by Jinan Pharmaceutical (Jinan, Shandong, China) as described by Zhang et al.[20] The water extract of the crude herbal materials was processed as described in the Pharmacopoeia of the People's Republic of China, 2000 edition.[19]

The resulting powder was formed into tablets, each tablet containing 3 g of the crude herbal mixture. The main ingredients of placebo are medical starch, edible caramel pigment (correcting color agent), bitter agent (the flavoring agent), both the placebo and herbal tablets were identical in shape, size, color and taste. Furthermore, to minimize the effect of the distinctive smell of herbal preparations on double blinding, the herbal tablets and placebo were all contained in blister packs made from plastic film and aluminium foil, with six tablets in each blister pack. The packs were distributed to the patients by a physician who was not involved in the study. The study investigators and patients were not aware of the identity of the administered medications.

2.3. Study procedures

A physician who was not involved in patient evaluation performed a computer-generated randomization procedure by using SPSS 15.0 software. The participants, based on the severity of the disease, age, gender were randomly allocated to two different treating groups in a 1:1 ratio.

The DHYZ and placebo treatments were commenced when the patients were transferred to the ward of rehabilitation centre. All patients were treated with rehabilitation under the standard regimen as needed including antiplatelet, liplowering, antihypertensive, and antidiabetic medications. On top of rehabilitation and standard treatment, patients involved in this study received either DHYZ (18 g, twice daily) or placebo (18 g, twice daily) for 12 weeks.

During the study period, patients also received inpatient rehabilitation therapy consisting of 2 h of individual physiotherapy and 2 h of occupational therapy on 6 days each week.

2.4. Patient evaluation

Patients were assessed at baseline and after 4, 8 and 12 weeks' treatment with DHYZ or placebo. The motor function scores of patients were assessed by the Fugl-Meyer assessment (FMA) scale. The maximum score is 66 points for the upper extremity, 34 points for the lower extremity. Patients were categorized into 3 grades according to their baseline FMA score at initiation of this trial: severe (0–50), moderate (50–84), and mild (85–99).[21]

Activities of daily living (ADL), which was scored by Barthel index.[22] (Range 0–100; the higher the score, the greater the independence in ADL), was also assessed. Besides the neurological evaluation, all patients underwent electrocardiogram, blood routine, urine routine, renal function test, liver function test, electrolytes, prothrombin time (PT), and partial thromboplastin time (PTT) at first and every 4 weeks.

Side effects and tolerability were assessed by recording adverse events at each visit. All adverse events – reported, elicited, or observed – were recorded on the case report form, including the