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Research Paper

The effectiveness and safety of a danshen-containing Chinese herbal medicine for diabetic retinopathy: A randomized, double-blind, placebo-controlled multicenter clinical trial

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ABSTRACT

Ethnopharmacological relevance: *Salvia miltiorrhiza* (Danshen in Chinese) is a common traditional Chinese herbal medicine often used to treat many medical conditions. The Compound Danshen Dripping Pill (CDDP) is a danshen-containing Chinese herbal product for the treatment of cardiovascular diseases. However, to date, no controlled clinical studies have been conducted to evaluate the effects of CDDP on diabetic retinopathy (DR).

Aim of the study: The present large-scale clinical trial was designed to assess the effectiveness and safety of CDDP in treating patients with non-proliferative diabetic retinopathy (NPDR).

Materials and methods: 223 NPDR patients were enrolled in this controlled trial. Subjects received oral study medications three times daily for 24 weeks. The four groups were placebo, low-dose (270 mg), mid-dose (540 mg) and high dose (810 mg herbal medicine). Primary endpoints were changes in fluorescence fundus angiography (FFA) and fundoscopic examination parameters.

Results and discussion: At 24 weeks, for the FFA, the percent of "Excellent" and "Effective" in the high-dose and mid-dose CDDP groups was 74% and 77%, respectively, very significantly higher than 28% in the placebo group ($P < 0.001$). For fundoscopic examination, the percent of "Excellent" and "Effective" in the high-dose and mid-dose CDDP groups was 42% and 59%, respectively, very significantly higher than 11% in the placebo group ($P < 0.001$). No adverse events with clinical significance were observed.

Conclusions: DR is a severe microvascular complication of diabetes and a major cause of adult blindness worldwide. Our clinical trial data demonstrated the therapeutic value and safety of a danshen-containing Chinese herbal medicine in patients with diabetic retinopathy.

1. Introduction

Diabetic retinopathy (DR), a severe microvascular complication of diabetes (Congdon et al., 2003), is a major cause of adult blindness worldwide. The prevalence of DR in China for individuals over 60 years of age is approximately 16%, and its incidence is 8.38/1000 person-years (Li and Wang, 2013). Treatment of DR includes medical management to control blood sugar, blood pressure and serum lipids, ocular management, and adjunctive pharmacologic therapies (Schwartz and Flynn, 2007; Simó and Hernández, 2009; ACCORD

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Study Group, ACCORD Eye Study Group, 2010). However, these approaches for DR management have limitations including invasive procedures and side effects of drug therapy (Schwartz and Flynn, 2007; Simó and Hernández, 2009; Feng et al., 2014). To date, there are no measures to effectively control the progression of DR. Thus, there is a strong motivation for exploring alternative strategies, including the use of Chinese herbal medicines, in DR therapeutics.

Salvia miltiorrhiza (Danshen in Chinese) is a very commonly used traditional Chinese herbal medicine. Compound Danshen Dripping Pill (CDDP) is a Chinese herbal medicine product used for the treatment of cardiovascular diseases (Chu et al., 2011). It contains the extract from danshen (*Salvia miltiorrhiza*), notoginseng (*Panax notoginseng*; or Sanchi in Chinese), and borneol. These three traditional Chinese medicines have been used for over a thousand years to treat many medical conditions. The CDDP promotes blood circulation and alleviates pain (Chu et al., 2011). Based on the theory of traditional Chinese medicine (TCM), the pathogenesis of DR is due to blood stasis that damages collateral vessels in the eye (Duan et al., 2011). Published animal experiments using different animal models and clinical trials in DR patients have demonstrated that CDDP can improve the symptoms of DR (Zhou et al., 2002, 2006; Qi et al., 2007; Yang et al., 2013). In addition, CDDP has been studied in different body systems with a good safety record (H. Xu et al., 2014; Yang et al., 2014). However, to date, no controlled clinical trial has been conduced to evaluate the effects of CDDP on DR.

In the present study, a randomized, double-blind, placebo-controlled, dose-ranging and multicenter clinical trial was conducted. We recruited glycemic-controlled DR patients with non-proliferative diabetic retinopathy (NPDR). These subjects were randomly assigned into four groups, and they received either placebo or three different doses of CDDP to explore the optimal therapeutic dose. The primary endpoints were changes in fluorescence fundus angiography (FFA) and fundoscopic examination parameters after 24 weeks of CDDP treatment. In addition, corrected visual acuity, intraocular pressure, glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG) were obtained in these subjects. The safety profile of the CDDP in the study subjects was also collected.

2. Materials and methods

2.1. Study subjects

The research protocol was approved by the local Medical Ethics Commission in China, and was implemented in accordance with the provisions of the Declaration of Helsinki.

The inclusion criteria were as follows: (1) Subjects were 30–70 years old. (2) Subjects were diagnosed with NPDR (American Association of Ophthalmology, 2006). (3) Subjects were on a stable oral hypoglycemic treatment for at least three months. (4) Subjects signed written informed consent.

Exclusion criteria were as follows: (1) Subjects had HbA1c level $>8\%$. (2) Subjects were treated with retinal photocoagulation or suitable for laser photocoagulation with proliferative diabetic retinopathy in one eye or both eyes. (3) Subjects were taking DR medications. (4) Subjects had other eye diseases, including glaucoma, with cataracts affecting fundoscopic examination. (5) Subjects had received cataract surgery within the previous 3 months. (6) Subjects had non-diabetic retinopathy, uveitis, retinal detachment, optic nerve diseases or highly myopic eyes. (7) Subjects had significant cardiovascular, liver, kidney, or hematopoietic systems diseases, mental illness, and other serious medical conditions. (8) Subjects had diabetic nephropathy with kidney failure. (9) Subjects were pregnant, planning to become pregnant, or lactating. (10) Subjects were allergic to Chinese herbal medicines. (11) Subjects had participated in any other clinical trials in the previous month.

2.2. Botanical materials

The study's herbal drug, Compound Danshen Dripping Pill (CDDP) was obtained from the Tasly Pharmaceutical Group Co., Tianjin, China. The CDDP contains the extract from danshen (*Salvia miltiorrhiza*), notoginseng (*Panax notoginseng*) and borneol.

2.3. Study protocol

After an initial screening visit, 223 glycemic-controlled patients with NPDR were recruited from 10 clinical research centers in China. All subjects received standard treatment without any diet intervention. A stratified, block randomization method was conducted by a biostatistician. Patients were assigned into four groups receiving placebo ($n=56$), low-dose CDDP ($n=56$), mid-dose CDDP ($n=56$) and high-dose CDDP ($n=55$) (Fig. 1).

Subjects were orally administered study medications with plain water three times daily. Each CDDP pill contains 27 mg of herbal medicine. For each administration, subjects in the placebo group received 30 placebo pills, subjects in the low-dose CDDP group received 10 CDDP pills plus 20 placebo pills (270 mg herbal medicine), subjects in the mid-dose CDDP group received 20 CDDP pills plus 10 placebo pills (540 mg herbal medicine), and subjects in the high-dose CDDP group received 30 CDDP pills (810 mg herbal medicine). Placebo pills, which contained starch and caramel, had the same appearance as the CDDP pills, and were

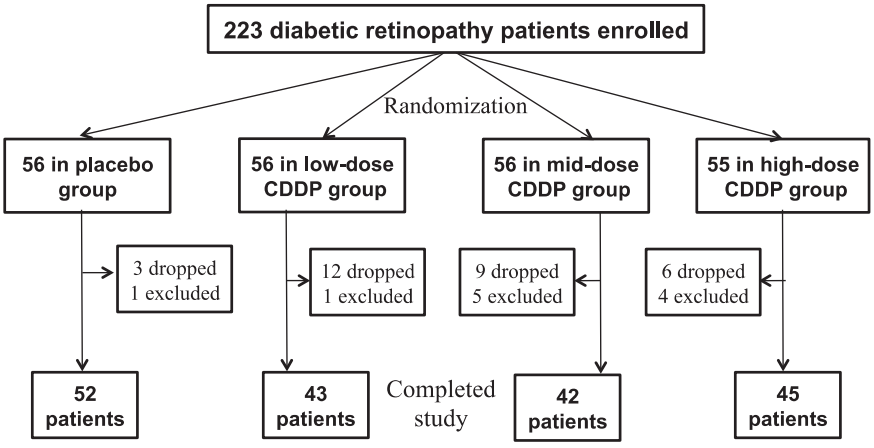

Fig. 1. Flow diagram of study subjects randomization and the completion of the trial.