

Improvement of accessory symptoms of hypertension by TSUMURA Orengedokuto Extract, a four herbal drugs containing Kampo-Medicine Granules for ethical use: A double-blind, placebo-controlled study

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Received 8 January 2004; accepted 17 February 2004

Abstract

A double-blind, placebo-controlled study was conducted to evaluate the efficacy, safety, and utility of TSUMURA Orengedokuto Extract Granules for Ethical Use (TJ-15) as a treatment for the accessory symptoms of hypertension. Two capsules of the study drug were administered orally 3 times daily (i.e., before meals) for 8 weeks.

Among 265 patients enrolled in the study, 134 were assigned to the TJ-15 group and 131 were assigned to the placebo group, of whom 204 patients (103 in the TJ-15 group and 101 in the placebo group) were included in the efficacy and utility analyze and 251 patients (128 in the TJ-15 group and 123 in the placebo group) were included in the safety analysis.

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Efficacy was significantly higher in the TJ-15 group based on the total score for the accessory symptoms of hypertension which was the primary efficacy endpoint (Wilcoxon's rank sum test, $p = 0.013$).

When each accessory symptom of hypertension was assessed separately, efficacy was higher for hot flushes and facial suffusion in the TJ-15 group (Wilcoxon's rank sum test, $p = 0.034$, and 0.022 , respectively).

There were no significant differences between the TJ-15 and the placebo groups with respect to the decrease of blood pressure or the antihypertensive effect.

There was also no significant difference between the two groups with regard to the overall safety rating.

The utility rating was significantly higher in the TJ-15 group than in the placebo group (Wilcoxon's rank sum test, $p = 0.016$).

In conclusion, TJ-15 was superior to placebo with respect to efficacy, safety, and utility for the treatment of accessory symptoms of hypertension.

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Keywords: Orengedokuto; Kampo medicine (Japanese herbal medicine); Double-blind; Placebo-controlled study; Accessory symptoms of hypertension

Introduction

Evidence has been provided by many epidemiological studies that hypertension is a major risk factor for cardiovascular disease and is closely related to the survival of patients. The treatment of hypertension is in high social need. A comprehensive strategy for anti-hypertensive therapy, including diet, exercise, and medications is widely recommended by many Guidelines including those released by the [Guidelines subcommittee of Japanese Society of Hypertension \(2000\)](#).

On the other hand, hypertension per se is almost asymptomatic so that the patient's quality of life (QOL) is less impaired by hypertension than by other diseases. However, since the treatment of hypertension needs to be continued over the long term, it is important that due consideration be given to the patient's QOL. According to Dimenas et al., higher blood pressure is associated with an increase of emotional problems, sleep disorders, cardiac and gastrointestinal symptoms, and dissatisfaction (Dimenas et al., 1989). The modern lifestyle is stressful and the relationship between stress and hypertension has attracted considerable attention. It has been pointed out that symptoms of hypertension, such as "anger," "tension," "anxiety," and "worries," are partly responsible for hypertension because they cause an increase of sympathetic activity. Attention should also be paid to the impairment of QOL by the adverse effects of antihypertensive therapy. Taken together, the control of symptoms in hypertensive patients cannot be ignored because it may not only improve the QOL but also help to control the blood pressure.

Orengedokuto is a Kampo medicine (Japanese herbal medicine) that has long been used for the treatment of facial suffusion, a burning sensation, headache, excitation, anxiety, and irritability (Otsuka et al., 1986). In clinical practice, Orengedokuto is currently used for the treatment of palpitations, excitement, hot flushes, facial

suffusion, and neurosis. The present communication is a report of a double-blind, placebo-controlled study that was conducted to assess the usefulness of Tsumura Orengedokuto Extract Granules for Ethical Use (TJ-15) for management of the accessory symptoms of hypertension. TJ-15 has already been approved by the Japanese Health, Labour and Welfare as an ethical drug.

Patients and methods

Patient selection

The subjects were selected from among patients with essential hypertension who met all the inclusion criteria and did not fit any of the exclusion criteria (Table 1).

Methods

The protocol of this study is summarized in Fig. 1.

A double-blind, placebo-controlled trial was performed in 2 groups of patients from June 1994 to March 2001. Patients were randomized to the study medications, and the blinding was ensured by the controller (Shuji Takaori). Informed consent was obtained from each patient before entry into the observation period. Following the 4-week observation period, 2 capsules of TJ-15 or the placebo were administered orally to each patient 3 times daily (i.e., before meals) for 8 weeks. Each capsule of TJ-15 contained 0.25 g of a spray-dried powdered extract of Orengedokuto (Tsumura & Co., Japan). The powder was obtained by hot water extraction of the following four medicinal herbs blended at a ratio of 3:2:2:1.5: Scutellariae radix (the root of *Scutellaria baicalensis* Georg stripped of its periderm), Coptidis rhizoma (the rootstock of *Coptis japonica* Makino stripped of its roots), Gardeniae fructus (the fruit of

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