A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of the Chinese Herbal Medicine “Ba Wei Di Huang Wan” in the Treatment of Dementia

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OBJECTIVES: To evaluate whether a traditional Chinese herbal medicine, ba wei di huang wan (BDW), improves cognitive and physical functioning in dementia patients.

DESIGN: An 8-week randomized, double-blind, placebo-controlled trial.

SETTING: Long-term-care facility in Japan.

PARTICIPANTS: Thirty-three patients with mild to severe dementia (7 men and 26 women; mean age ± standard deviation = 84.4 ± 7.8) were recruited and enrolled from May 2002 through September 2002.

INTERVENTION: Participants were randomly assigned to the active drug (BDW) group (n = 16) or the placebo group (n = 17) and treated for 8 weeks.

MEASUREMENT: Cognitive function and activities of daily living (ADLs); pulsatility index.

RESULTS: After the trial, cognitive function as assessed using the Mini-Mental State Examination (MMSE) significantly improved from 13.5 ± 8.5 to 16.3 ± 7.7 (P < .01, 95% confidence interval (CI) = −4.1 to −1.4) in the BDW group. The ADL score in the Barthel Index also significantly changed, from 61.8 ± 34.6 to 78.9 ± 21.1 (P < .01, 95% CI = −26.2 to −7.9). In contrast, MMSE and Barthel Index scores of the placebo group showed no significant change. Eight weeks after the end of the administration, MMSE and Barthel Index scores of the BDW group declined to the baseline level. The pulsatility index in the internal carotid artery as measured using Doppler sonography significantly decreased in the BDW group (2.5 ± 1.7 to 1.9 ± 0.5, P < .05) but not in the placebo group.


Key words: dementia; Chinese herbal medicine; complementary medicine; MMSE; ADL

Because cholinergic deficits are thought to be associated with cognitive decline or dementia, augmentation of the central cholinergic system by selective inhibition of central nervous system cholinesterase is a current therapeutic strategy for Alzheimer’s disease (AD). However, in spite of such recent advances, therapeutic windows for AD and other dementing disorders are still narrow and limited in comparison with other common disorders in the elderly.

Herbal medicine is an increasingly common form of complementary and alternative therapy. Recent clinical studies have demonstrated that some herbal medicines show benefits for dementia. A traditional Chinese herbal medicine, ba wei di huang wan (BDW; hachimi-jio-gan in Japanese, meaning eight ingredient pill with Rehmannia) has been empirically used for the elderly who have fatigue, cold sensation, lumbago, and reduced muscle strength and has a long history as a remedy for the elderly with cognitive decline and disability. Moreover, recent animal studies showed that BDW improved scopolamine-induced memory impairment, although its beneficial effects were not proven in a well-controlled clinical study.

For this study, a randomized, double-blind, placebo-controlled clinical trial of BDW in the treatment of dementia was designed.
TABLE 1. Clinical and Demographic Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ba Wei Di Huang Wan</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male:female)</td>
<td>3:13</td>
<td>4:13</td>
<td>&gt;.5</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>85.6 ± 6.4</td>
<td>83.5 ± 9.3</td>
<td>&gt;.5</td>
</tr>
<tr>
<td>Diseases</td>
<td>15 AD with CVD; 1 AD</td>
<td>15 AD with CVD; 2 AD</td>
<td></td>
</tr>
<tr>
<td>Duration of illness, years, mean ± SD</td>
<td>5.5 ± 0.6</td>
<td>5.2 ± 0.4</td>
<td>&gt;.5</td>
</tr>
<tr>
<td>Baseline Mini-Mental State Examination score, mean ± SD</td>
<td>13.5 ± 8.5</td>
<td>16.8 ± 6.3</td>
<td>&gt;.5</td>
</tr>
<tr>
<td>Baseline Barthel Index, mean ± SD</td>
<td>61.8 ± 34.6</td>
<td>68.5 ± 6.1</td>
<td>.40</td>
</tr>
<tr>
<td>Blood pressure, mmHg, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>128.0 ± 25.0</td>
<td>126.8 ± 11.6</td>
<td>&gt;.5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73.0 ± 6.2</td>
<td>76.0 ± 7.4</td>
<td>&gt;.5</td>
</tr>
<tr>
<td>Pulsatility index, mean ± SD</td>
<td>2.5 ± 1.7</td>
<td>2.4 ± 2.2</td>
<td>&gt;.5</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease; CVD = cerebrovascular disease.

METHOD

Participants

All dementia subjects were recruited from Akiba Hospital, a long-term care facility located in Chiba prefecture, Japan. The diagnosis of dementia was made in 50 patients according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, criteria. Physical conditions of all patients had been stable for the previous year. At baseline, each patient received a uniform evaluation that included a medical history, a physical and neurological examination, and a brain computed tomography scan, as well as assessments of cognitive function and activities of daily living (ADLs).

Cognitive function and ADLs were assessed using the Mini-Mental State Examination (MMSE) and the Barthel Index, respectively. Patients who had serious behavioral problems that required neuroleptics, a major medical illness such as neoplastic disease, or any other disease that would be likely to prevent completion of this study were excluded. Patients who had been treated with cholinesterase inhibitors were also excluded. As a result, 33 patients (7 men and 26 women; mean age ± standard deviation (SD) = 84.4 ± 7.8) with mild to severe dementia (MMSE score of 0–25) were selected. Only 11 (33%) of the patients reported a clinical history of stroke. Nonetheless, 30 (91%) had objective evidence of ischemic cerebrovascular disease (CVD) (mostly subcortical lacunae and white matter change) ascertained using neuroimaging or clinical evidence of CVD using neurological examination. These cases were diagnosed with AD with CVD (n = 30, 91%) as distinct from pure AD (n = 3, 9%). No case was felt to have vascular dementia in the absence of clinically significant AD.

Patients with a well-controlled common disease such as hypertension, diabetes mellitus, or hypercholesterolemia were included. Sedatives were avoided as much as possible. Hypnotics were allowed occasionally.

The local institutional review board approved the protocol, and written informed consent was obtained after a full explanation to responsible caregivers together with the patient.

Intervention Protocol

An 8-week randomized, double-blind, placebo-controlled trial was conducted from May 2002 through September 2002. Participants were randomly assigned to the active drug (BDW) group (15 AD with CVD and one pure AD) or the placebo group (15 AD with CVD and two pure AD) using a table of random numbers (Table 1).

BDW, which is approved for medical use in Japan, was purchased from Uchida Wakanayaku Co. Ltd. (Tokyo, Japan). It consists of eight herbs: 8 g of Rheum annua Lutinsa Libosch. var. purpurea Makino (Scrophulaxiaceae); 4 g of Cornus officinalis Sieb et Zucc (Cornaceae); 4 g of Dioscorea batatas Dence (Dioscoreaceae); 3 g of Alisma orientale Juzep (Alimataccae); 3 g of Poria cocos Wolf (Poriacea) 3 g of Paeonia suffruticosa Andr. (Paeoniaceae) 1 g of Cinnamomum cassia Blume (Lauraceae); and 1 g of Aconitum carmichaeli Debx. (Ranunculacea). A powdered mixture of these herbs with honey was made into pills of 0.1 g, 4-mm diameter. The placebo was made from black rice powder, sepia, and honey in the same way at the same factory. The controller (J-CC) guaranteed that the active drugs and the placebo could not be discriminated from each other.

Participants were administrated 20 pills (2 g) of BDW or placebo 3 times a day after meals for 8 weeks.

Outcome Measure

All outcome measurements were performed blind to the active drugs or placebo.

MMSE and the Barthel Index were administered 3 times: at baseline, at the end of the 8-week clinical trial, and at 8 weeks after completion of the protocol.

The mean, systolic, and diastolic velocities were measured in left internal carotid artery using Doppler sonography (Logic 500 Pro, with 8.8-MHz probe LA39, GE Yokogawa Medical Systems, Tokyo, Japan), and the pulsatility index (PI) was calculated at baseline and the end of trial.

Statistical Analysis

Changes in MMSE and Barthel Index scores from baseline (mean ± SD) were compared using the Tukey-Kramer post hoc test with repeated measures of analysis of variance (ANOVA). Other data between the baseline and the endpoint were also compared using a paired t test. P < .05 was required for statistical significance.
RESULTS
All of the 33 patients completed the protocol. Adverse reactions to BDW such as stomach discomfort, diarrhea, eczema, or palpitation (tachycardia) were not observed. Three patients in the BDW group withdrew during the observation period after administration. Of the three, one was transferred to another facility for social reasons, and two had complications: urinary tract infection and an upper respiratory tract infection.

As shown in Figure 1, the MMSE score in the BDW group had improved significantly at the end of drug administration in comparison with baseline (Tukey-Kramer post hoc test with repeated measures of ANOVA, \( P < .01 \)). After 8 weeks of administration, the mean score increased by 2.6 (95% confidence interval (CI) = \(-4.1\) to \(-1.4\)) in the BDW group, whereas it increased by only 0.6 (95% CI = \(-2.0\) to \(-0.8\), no significance) in the placebo group. Notably, there were significant improvements in the serial 7s and three-word recall subscales in the BDW group (\( P < .05 \)). Furthermore, in the BDW group, the Barthel Index significantly improved at the end of drug administration in comparison with that at baseline (Figure 2, the Tukey-Kramer post hoc test \( P = .01 \)). After 8 weeks of administration, the mean Barthel Index in the BDW group increased by 18.3 (95% CI = \(-27.1\) to \(-9.5\)), whereas that in the placebo group increased by only 0.4 (95% CI = \(-3.8\) to \(-3.1\)).

PI was significantly decreased in the BDW group (2.5 ± 1.7 to \(1.9\) ± 0.5, \( P < .05 \)) but not in the placebo group (2.4 ± 2.2 to \(2.0\) ± 1.3). Blood pressure (128.0 ± 25.0/73.0 ± 6.2 to 124.0 ± 20.2/75.9 ± 4.4 in the BDW group, 126.8 ± 11.6/76.0 ± 7.4 to 125.3 ± 13.2/76.4 ± 8.5 in the placebo group) did not significantly change in either group.

DISCUSSION
Despite the limitation of small sample size, this preliminary, double-blind, randomized, placebo-controlled trial suggested that BDW enhanced cognitive function and ADL abilities of elderly patients with dementia.

BDW is one of the most common recipes in traditional Chinese, Japanese, and Korean medicines and has been used in a large number of elderly patients for 2,000 years.5,6 The administration and safety of BDW have been clinically established, but the beneficial effects upon cognitive decline and disability have not been established in a controlled clinical trial.

One possible explanation of BDW’s effect is that it is mediated through the central cholinergic system. Studies have documented that BDW enhances choline acetyltransferase activity and increases the acetylcholine content of the frontal cortex in a rat model of scopolamine-induced memory impairment.7,8 This suggests that the effects of BDW on the cognitive functions are at least partly related to the central cholinergic system in a way similar to donepezil, but cognitive improvement with BDW is much greater than with cholinesterase inhibitors. MMSE in BDW groups increased by a mean of 2.6 points, approximately corresponding to 5 points on the Alzheimer’s Disease Assessment scale. Moreover, BDW improved ADLs more markedly than cognitive function. Even patients showing only a 1- or 2-point improvement on the MMSE became quick in their action and response to caregivers. Nurses and families felt that the patients looked cheerful. These facts suggest that there might be other mechanisms of cognition improvement with BDW. Because PI initially reflects vascular resistance,14 the decreased PI value after treatment with BDW presumably represents a decrease in cerebrovascular resistance. It was recently reported that BDW increased the flow velocity in the central retinal arteries as measured using Doppler sonography in healthy young adults.13 Therefore, BDW also has the potential to improve the cerebral blood flow, but because BDW is a mixture of eight herbs, many other unknown mechanisms can be surmised. A traditional Chinese medicine is not simply a purified substrate but contains
many ingredients, and the interaction of these ingredients is important. Eight herbs in BDW were carefully devised to interlock according to the traditional rules. It could be that these characteristics of BDW as a traditional Chinese medicine may have contributed to the large magnitude of the effect in the present study.

A major limitation of this study is the small sample size. Therefore, the effects of BDW on AD could not be analyzed separately from its effect on CVD. Most of the patients in the study had AD with CVD because of their long duration of illness. To resolve these questions, a long-term study of BDW with a larger sample size is needed.

In summary, this pilot study suggests that BDW therapy was a well-tolerated and effective treatment for dementia patients. BDW can be a new beneficial candidate to widen therapeutic options for treating dementia.

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REFERENCES