A Randomized, Observer-Blind, Controlled Trial of the Traditional Chinese Medicine *Yi-Gan San* for Improvement of Behavioral and Psychological Symptoms and Activities of Daily Living in Dementia Patients

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Objective: This randomized, observer-blind, controlled trial examined the efficacy and safety of the traditional Chinese herbal medicine *Yi-Gan San* (YGS, *Yokukan-San* in Japanese) in the improvement of behavioral and psychological symptoms of dementia (BPSD) and activities of daily living (ADL).

Method: Fifty-two patients with mild-to-severe dementia (24 men and 28 women, mean ± SD age = 80.3 ± 9.0 years) according to DSM-IV criteria were investigated. Participants were randomly assigned to the YGS group (N = 27) or control (drug-free) group (N = 25) and treated for 4 weeks. The Neuropsychiatric Inventory (NPI) for the assessment of BPSD, the Mini-Mental State Examination (MMSE) for cognitive function, and the Barthel Index for ADL were administered at baseline and the end of the treatment. The frequency of extrapyramidal symptoms (EPS) and other adverse events was recorded. If patients showed insufficient response to treatment after 1 week, tiapride hydrochloride, a dopamine D_1 selective neuroleptic, was added to the regimen. Data were collected from January 2004 to March 2004.

Results: All participants in both groups completed the trial. In the control group, 11 patients required treatment with tiapride hydrochloride. Significant improvements in mean ± SD NPI (from 37.9 ± 16.1 to 19.5 ± 15.6) and Barthel Index (from 56.4 ± 34.2 to 62.9 ± 35.2) scores were observed in the YGS group, but not in the control group. MMSE results were unchanged in both groups. EPS were not observed in either group, but dizziness and impaired postural sway were observed in 6 patients treated with tiapride hydrochloride.

Conclusion: *Yi-Gan San* improves BPSD and ADL. Follow-up studies using a double-blinded, placebo-controlled design are recommended.

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Behavioral and psychological symptoms of dementia (BPSD) are commonly seen in patients with Alzheimer's disease (AD) and other forms of senile dementia. BPSD are a significant burden to caregivers and a major reason for the early institutionalization of AD patients.[1] Moreover, they consistently relate to poor performance of activities of daily living (ADL).[2] Pharmacologic interventions including antipsychotics[3] and acetylcholine esterase inhibitors (AChEIs)[4] have been investigated, but drug-induced extrapyramidal symptoms (EPS) and other adverse events are not uncommon consequences among elderly people.[5]

For millennia, herbal medicines have been used with apparent safety and efficacy in Asia, including present-day China, Korea, Taiwan, and Japan, for alleviating various symptoms of senile dementia. We have previously reported the clinical efficacy and safety of such medicines in cognitive function and ADL in AD.[6,7]

Yi-Gan San (YGS, *Yokukan-San* in Japanese, *Pulvis depressionis efficientiae*) was developed in 1555 by Xue Kai as a remedy for restlessness and agitation in children. Prompted by the increasing life expectancy of the Japanese population, geriatricians have begun to use this traditional regimen for BPSD in the elderly. For example,

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Table 1. Baseline Characteristics of 52 Patients With Dementia[a]

Characteristic	YGS Group	Control Group
Sex, N, male:female	13:14	11:14
Age, mean ± SD, y	77.0 ± 9.6	84.0 ± 6.7
Diagnoses, N		
Alzheimer's disease	14	16
Vascular dementia	6	3
Alzheimer's disease with CVD	1	2
Dementia with Lewy bodies	6	4
Duration of illness, mean ± SD, mo	67.0 ± 6.3	66.0 ± 9.1
Test scores, mean ± SD		
Neuropsychiatric Inventory	37.9 ± 16.1	33.6 ± 20.1
Mini-Mental State Examination	13.2 ± 8.5	11.3 ± 9.6
Barthel Index	56.4 ± 34.2	55.4 ± 31.0

[a]There were no significant differences between groups for any of the characteristics.
Abbreviations: CVD = cerebrovascular disease, YGS = *Yi-Gan San*.

Tahara et al.[8] reported 2 cases in an extended care unit who were successfully treated with YGS for BPSD. Tsunekawa and colleagues[9] reported the efficacy of a YGS derivative (*Yi-Gan San jia Chenpi Banxia, Pulvis depressionis efficientiae cum Pinellia et aurantio)* in 7 cases of demented elderly patients with nighttime disturbance, disinhibition, eating disturbance, anxiety, hallucinations, irritability, and insomnia. Such detailed case observations, depending on the traditional Chinese medicine studied, can offer hints at new treatments for currently incurable diseases. Therefore, based upon these observations, we designed a randomized, observer-blind, controlled trial to assess the efficacy and safety of YGS in the improvement of BPSD and ADL.

METHOD

Participants

All subjects were recruited from 3 centers for long-term care located in the prefectures of Yamagata, Iwate, and Miyagi, Japan. Data were collected from January 2004 to March 2004. The diagnosis of dementia was made for a total of 60 patients according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria.[10] The physical condition of all patients had been stable for the past year. At baseline, each patient received a uniform evaluation, which included a medical history, physical and neurologic examination, and brain computed tomography scan, as well as the Mini-Mental State Examination (MMSE)[11] to assess cognitive function and the Barthel Index for ADL (higher scores indicate better performance).[12] BPSD were assessed and evaluated using the Neuropsychiatric Inventory (NPI: lower scores indicate better performance).[13]

We included patients who satisfied the following criteria: (1) dementia of Alzheimer's disease (DSM-IV), vascular dementia (as defined by the NINDS-AIREN International Workshop),[14] dementia with Lewy bodies,[15] or Alzheimer's disease with cerebrovascular disease; (2) an MMSE score of < 24; and (3) concomitant BPSD with an NPI score of > 6 on at least one of the delusion, hallucination, violent behavior, or apathy subscales. The exclusion criteria were (1) major medical illness such as neoplastic disease, acute inflammation, or any other disease that would be likely to prevent completion of this study; (2) other types of dementia (such as Korsakoff syndrome); (3) delirium due to drug use, metabolic intoxication, or inflammation; (4) an MMSE score ≥ 24; (5) neuroleptic treatment at baseline; and (6) AChEI (donepezil) therapy within 1 year.

Intervention

Of the 60 patients enrolled according to the criteria above, 8 subjects were excluded because of inflammation (2 cases), use of neuroleptics (5 cases), and drug-induced delirium (1 case). Therefore, 52 patients with mild-to-severe dementia (24 men and 28 women, mean ± SD age = 80.3 ± 9.0 years, MMSE score of 0–23) were investigated. Written informed consent was obtained from participants or their families following a detailed explanation of the study. The Institutional Review Board of Tohoku University (Sendai City, Japan) approved the study. The patients were stratified for NPI, MMSE, Barthel Index, age, and sex and then randomly assigned to the YGS treatment group (N = 27) or the control group (N = 25) using a random number table. Patient characteristics are shown in Table 1. There was no significant difference in the characteristics between the 2 groups.

The mixture of dried plants—4.0 g of *Atractylodis Lanceae* rhizoma, 4.0 g of Hoelen, 3.0 g of Cnidii rhizoma, 3.0 g of Angelicae radix, 2.0 g of Bupleuri radix, 1.5 g of Glycyrrhizae radix, and 3.0 g of Uncariae ramulus et uncus—was added to 700 mL of distilled water and boiled for 1 hour, filtered, and then concentrated to 300 mL. This decoction was lyophilized to yield 4.5 g of dry extract and was added to 3.0 g lactate to yield a total of 7.5 g of powder for 1 day's use. This powder is registered in the Pharmacopoeia of Japan as the Kampo Medicine TJ-54 *Yokukan-San* and was provided by Tsumura Co, Ltd (Tokyo, Japan). The quality was standardized based on the Good Manufacturing Practice defined by the Ministry of Health and Welfare of Japan. Moreover, Tsumura Co, Ltd, standardized the quality of its TJ-54 Yokukan-San by 3D-HPLC (high-performance liquid chromatography) analysis.

Participants in the YGS group each received 2.5 g of YGS powder (1.5 g of extract) 3 times a day before meals for 4 weeks. If patients showed insufficient response to the treatment after 1 week, 25 mg of tiapride hydrochloride, a dopamine D_1 selective classical neuroleptic, was added to the regimen.

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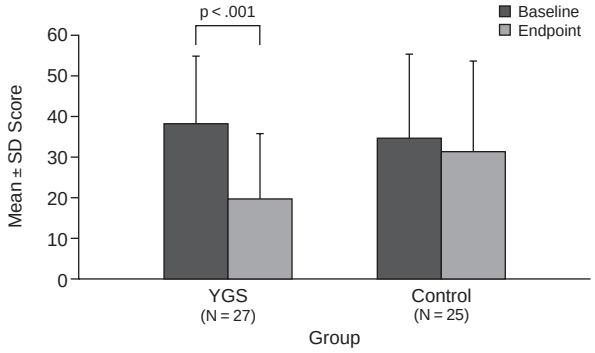
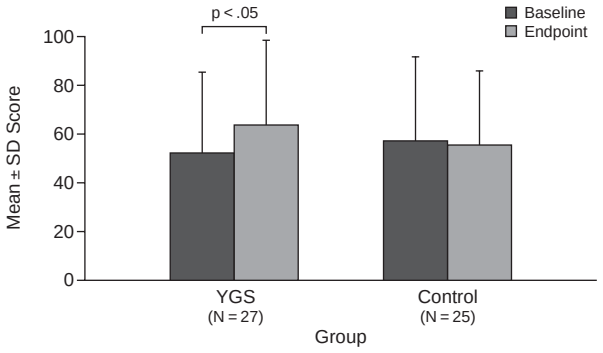
Figure 1. NPI Total Scores of 52 Patients With Dementia at Study Baseline and Endpoint



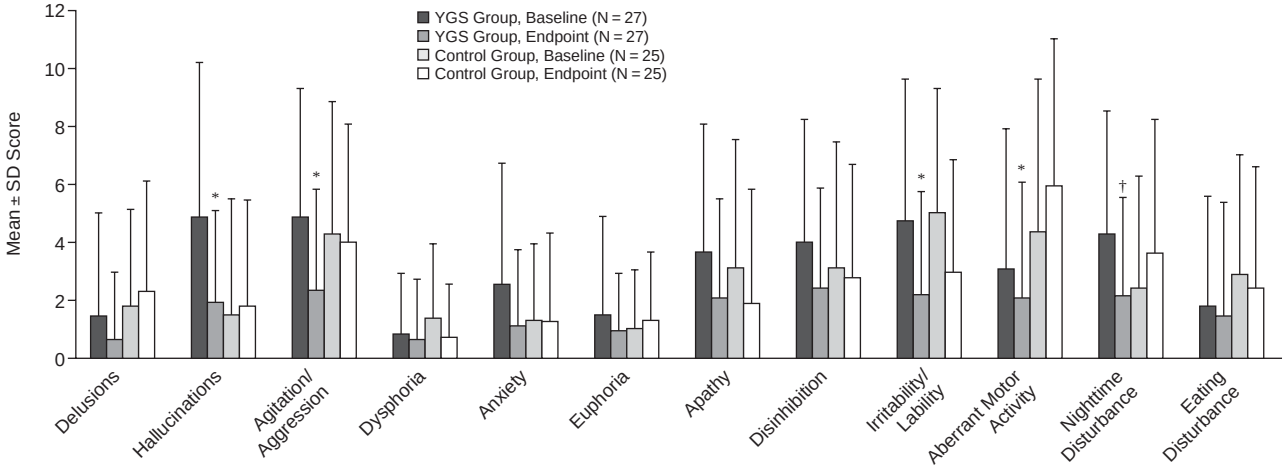
Abbreviations: NPI = Neuropsychiatric Inventory, YGS = *Yi-Gan San*.

Figure 2. Barthel Index Scores of 52 Patients With Dementia at Study Baseline and Endpoint



Abbreviation: YGS = *Yi-Gan San*.

Figure 3. NPI Subscale Scores of 52 Patients With Dementia at Study Baseline and Endpoint



*p < .05.
†p = .06.
Abbreviations: NPI = Neuropsychiatric Inventory, YGS = *Yi-Gan San*.

Outcome Measure and Statistical Analysis

A trained nurse performed the NPI, MMSE, and Barthel Index tests in a manner blinded to treatment status. All scales were examined at baseline and at the end of the 4-week interventions. Statistical analyses of the NPI, MMSE, and Barthel Index results were performed using repeated-measures analysis of variance and the Fisher protected least significant difference test. The frequency of EPS was measured according to the Barnes Akathisia Scale[16] (Japanese edition). However, as will be described later, none of the participants showed EPS during the observation period. Therefore, we analyzed the incidence of adverse events freely noted in both groups by χ^2 test. Results were considered to be statistically significant at $p < .05$. Data are expressed as mean ± SD.

RESULTS

All participants in both groups completed the trial. Significant improvements in the scores for both the NPI (from 37.9 ± 16.1 to 19.5 ± 15.6, $p < .001$; Figure 1) and the Barthel Index (from 56.4 ± 34.2 to 62.9 ± 35.2, $p < .05$; Figure 2) were observed in the YGS group, whereas these scores did not change significantly in the control group (NPI from 33.6 ± 20.1 to 31.0 ± 20.8; Barthel Index from 55.4 ± 31.0 to 51.7 ± 32.6). On the NPI subscales, significant improvements in hallucinations, agitation/aggression, irritability/lability, and aberrant motor activity were observed in the group treated with YGS (Figure 3). Nighttime disturbance showed a tendency to improve ($p = .06$). MMSE results did not

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change in either group (YGS group, from 13.2 ± 8.5 to 11.7 ± 7.6; control group, from 11.3 ± 9.6 to 12.0 ± 6.9).

In the control group, 11 patients had to be treated with tiapride hydrochloride. None of the patients in the YGS group required such additional therapies. EPS listed in the Barnes Akathisia Scale were not observed in either group, but dizziness and impairment of postural sway were observed in 6 cases treated with tiapride hydrochloride in the control group. No treatment-emergent adverse events were seen in either group during the observation period, but 2 participants who continued YGS therapy after the trial seemed to become oversedated. However, among these patients, the treatment was well tolerated when the dose was reduced from 4.5 g to 3.0 g per day.

DISCUSSION

Behavioral and psychological symptoms have a serious impact on the quality of life of dementia patients, as well as their caregivers. Recent trials demonstrated that AChEIs may also be useful, but are not completely effective.[17,18] Use of neuroleptics is also common in treating patients with BPSD, but neuroleptics have the drawback of being associated with EPS in elderly patients.[3] Moreover, neuroleptic treatment is a major risk factor for aspiration pneumonia[19] and falls[20] in elderly patients. Tiapride hydrochloride is widely used in Japan for the treatment of mild BPSD, but as shown in this study, the drug lacks efficacy and causes dizziness and postural imbalance, which can lead to falls. Thus, an effective drug therapy for BPSD has not previously been established.

In the present study, we showed that a traditional Chinese herbal medicine, YGS, significantly improved BPSD without significantly influencing cognitive function as assessed by the MMSE. In our daily clinical experience, the effect of YGS usually begins within 1 or 2 weeks of treatment. In addition to having a rapid onset of action, YGS also caused no serious adverse events. YGS has been used as a mild sedative. Aizawa et al.[21] reported that a YGS derivative was effective in the treatment of insomnia. Sedatives tend to have unfavorable effects on cognitive function,[22] but in the present study, MMSE results did not significantly change in the YGS group. Because the MMSE is not a sensitive measure of cognitive function, and due to a rather short-term observation period (2 months), we could not fully assess the influence of YGS on cognitive function.

Two cases seemed to become overly sedated when treated with the full daily dose (4.5 g) of YGS. However, in these patients, YGS was well tolerated when the dose was reduced to 3.0 g. One of these 2 patients briefly discontinued YGS therapy. Her NPI score had decreased from 25 at baseline to 8 with YGS treatment, but it increased to 10 after 1 month of abstention from treatment. Delusions and apathy were also diminished by YGS treatment but relapsed during the drug-free period. When YGS treatment (3.0 g per day) was resumed at the family's request, these symptoms vanished again. Symptoms seemed to be closely related to treatment status (on/off) in this case.

This study was performed in a single-blinded manner, i.e., the observer who collected the data was blinded to the treatment. A double-blind study could not be performed because we could not develop an adequate placebo, due to the distinctive taste and smell of YGS. The possibility of a placebo effect cannot be completely excluded, although it is unlikely considering the cognitive level of these patients. A more rigorous double-blind, placebo-controlled design is needed for follow-up studies.

Several prior studies have investigated the mechanism of action of YGS. Egashira and colleagues[23] found that YGS improved the scopolamine-induced disruption of spatial cognition in rats. Indeed, YGS derivatives have been reported to increase both choline acetyltransferase activity and acetylcholine levels in experimental animals.[24,25] YGS may therefore enhance cholinergic transmission by mechanisms similar to those of AChEIs. It remains to be determined whether YGS improves cognitive function. Although YGS has been reported to increase choline acetyltransferase, in our study, because the MMSE is not a sensitive measure of cognitive function, and due to a rather short-term observation period (2 months), we could not fully assess the influence of YGS on cognitive function.

YGS is not a simple preparation of medicine, as it contains many ingredients. It has multiple biological effects, and the interactions between ingredients can be important. The hooks of *Uncariae sinensis* contain oxyindole and indole alkaloids, known for their protective effects against glutamate-induced neuronal death in cultured cerebellar granule cells.[26] On the other hand, Angelicae radix, another important herb in YGS, is known for its effects on γ-aminobutyric acid (GABA) and serotonin receptors.[27] It is known that receptors of neurotransmitters such as GABA-A α_1 subunits decrease in the AD brain, while receptors of excitatory neurotransmitters such as glutamate are retained.[28] Zubenko et al.[29] showed that BPSD were associated with a significant reduction of serotonin in the presubiculum, which was accompanied by reduced levels of serotonin and 5-hydroxyindoleacetic acid in the remaining regions. Therefore, actions of the serotonergic system may also account for some of the therapeutic effects of YGS.

Each herbal constituent of YGS plays a particular role, and the preparation was carefully devised so that the components would act in an interlocking manner. Thus, the benefits of YGS may be attributable to the preparation as a whole rather to the sum of each of its ingredients. These pharmacologic properties of YGS, a traditional Chinese medicine, most likely account for its versatile physiologic effects and safety.

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YGS was approved by the Ministry of Health and Welfare of Japan as an ethical-use drug for medical treatments in 1986. YGS has not been marketed in the United States; however, all of the herbs contained in YGS can be obtained in the United States. It may therefore be possible to perform similar studies on this herbal mixture in the United States. In summary, our randomized, observer-blind, controlled trial suggests that YGS therapy is a well-tolerated and effective remedy that improves BPSD and ADL.

Drug names: donepezil (Aricept), scopolamine (Transderm Scop).

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