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Effects of yokukansan on behavioral and psychological symptoms of vascular dementia: An open-label trial

Ken Nagata [a,*], Eriko Yokoyama [b], Takashi Yamazaki [a], Daiki Takano [a], Tetsuya Maeda [a], Satoshi Takahashi [c], Yasuo Terayama [c]

[a] Department of Neurology, Research Institute for Brain and Blood Vessels, Akita, Japan
[b] Department of Rehabilitation, Akita Prefectural Center of Rehabilitation and Psychiatric Medicine, Daisen, Japan
[c] Department of Neurology, Iwate Medical University, Morioka, Japan

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ABSTRACT

Previous clinical trials suggest that the traditional Japanese medicine yokukansan has beneficial effects on the behavioral and psychological symptoms of dementia (BPSD). The present study was conducted to elucidate the efficacy of yokukansan on BPSD in patients with vascular dementia. Thirteen Japanese patients (9 men and 4 women) who were diagnosed as having vascular dementia (VaD) according to the diagnostic criteria of NINDS-AIREN were subjected to the open-label clinical trial in which yokukansan (7.5 g/day) has been given for 4 weeks. Their mean age was 71.2 ± 6.5 years. The BPSD was evaluated using the Neuropsychiatric Inventory (NPI), cognitive function was evaluated by the Mini-Mental State Examination (MMSE), the activities of daily living was evaluated by Barthel index (BI) and Disability Assessment for Dementia (DAD), and the extrapyramidal signs were evaluated by United Parkinson's Disease Rating Scale (UPDRS). The mean NPI was 33.0 ± 17.3 and 23.6 ± 13.9 for the baseline and after treatment, respectively. It was significantly improved after treatment ($p < 0.05$). In the NPI-subcategories, there was a significant improvement in agitation and disinhibition after the treatment. There was no significant change in MMSE, BI, DAD or UPDRS before and after the treatment. There was no adverse effect during the treatment period. The present results suggest that yokukansan is beneficial for the treatment of BPSD in VaD patients.

Introduction

Vascular dementia (VaD) is the second most common cause of dementia following Alzheimer's disease (AD), and thought to account for 15–20% of all dementia cases (Rockwood et al. 2000; Erkinjuntti et al. 1997). Although VaD has been thought as one of the treatable dementias because an improvement can be expected through the prevention of stroke recurrence, stepwise deterioration in cognitive function is commonly seen in VaD patients. In addition to the decline in overall cognitive function, behavioral and psychological symptoms of dementia (BPSD) frequently appear also in VaD patients. According to the recent multi-center studies, BPSD were reported in 92% of the VaD patients, and 12.6% of the initial symptom were BPSD in VaD patients (Nagata 2005; Staekenborg et al. 2010). Since these symptoms strongly influence on the patients' quality of life and increase burden of their families and caregivers, BPSD are thought to be the most distressing manifestations of VaD patients. In addition to the environmental and/or behavioral strategies, pharmacological interventions have been endeavored to treat BPSD in patients with dementia including VaD. Among the wide variety of the pharmacological agents, atypical antipsychotics currently have the best evidence for efficacy, although BPSD represents off-label indication. Warning has been issued about a possible increased risk of cerebrovascular events and mortality in dementia patients being treated with atypical antipsychotics such as risperidone and olanzapine, whereas atypical antipsychotics were reported to cause less extrapyramidal signs (EPS) as compared with the conventional antipsychotics (Rainer et al. 2007; Jeste et al. 2008; Kuehn 2008). Since elderly patients may have higher risk of stroke and EPS compared with younger patients, there has been a controversy concerning the therapeutic

Abbreviations: VaD, vascular dementia; AD, Alzheimer's disease; BPSD, behavioral and psychological symptoms of dementia; EPS, extrapyramidal symptoms; ADL, activities of daily living; 3D-HPLC, three-dimensional high-performance liquid chromatography; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; BI, Barthel Index; DAD, Disability Assessment for Dementia; UPDRS, Unified Parkinson's Disease Rating Scale; CBC, complete blood cell count.

* Corresponding author at: Department of Neurology, Research Institute for Brain and Blood Vessels, 6-10 Senshu-Kubota-Machi, Akita 010-0874, Japan.
Tel.: +81 18 833 0115; fax: +81 18 833 6006.
E-mail address: nagata@akita-noken.jp (K. Nagata).

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choice of antipsychotics in elderly patients presenting with BPSD. Especially, VaD patients are more vulnerable to stroke recurrence than those with other type of dementia, and the antipsychotic prescription will be limited in VaD patients.

Previous clinical studies suggested a clinical efficacy of traditional Japanese medicine yokukansan on BPSD in patients with AD and related disorders. The clinical efficacy and safety of yokukansan for improvement of cognitive function, BPSD, and activities of daily living (ADL) have been reported (Iwasaki et al. 2005; Shinno et al. 2007, 2008). In a randomized observer-blinded controlled trial, Iwasaki et al. showed a significant improvement in BPSD and ADL in 27 dementia patients including those with VaD. However, there was no systematic clinical report in which the efficacy of yokukansan on BPSD was evaluated in VaD patients. Our study may endorse the previous knowledge concerning the clinical indication of yokukansan to the treatment of BPSD in VaD patients. The present study was designed to elucidate the effects of yokukansan on BPSD in VaD.

Materials and methods

Yokukansan extract was provided by Tsumura & Co. (Tokyo, Japan). Yokukansan contains a mixture of dried herbs, 4 g of Atractylodis lanceae rhizoma, 4 g of Poria, 3 g of Cnidii rhizoma, 3 g of Angelicae radix (*Angelica acutiloba*), 2 g of Bupleuri radix, 1.5 g of Glycyrrhizae radix, and 3 g of Uncariae uncis cum ramulus. These herbs are registered in the Pharmacopoeia of Japan ver. 15. Similar active ingredients derived from the herbal medicines in extract powders have been confirmed to be contained by thin-layer chromatography analysis to those found in standard solutions for the herbal medicines. The developed plates were either examined by spraying with a 4-dimethylaminobenzaldehyde reagent or dilute sulfuric acid, or irradiated with ultraviolet light. Upon comparison with the standard solutions for the herbal medicines, one spot among the spots from the yokukansan extract showed the same color tone and *Rf* value. In addition, the amounts of active ingredients such as glycyrrhizin, saikosaponin b_2 and ferulic acid have been determined by high-performance liquid chromatography analysis and stable contents have been secured. The chromatographic conditions for glycyrrhizin were column: a stainless steel column packed with octadecylsilanized silica gel for liquid chromatography, mobile phase: a mixture of H_2O, CH_3CN and CH_3COOH, column temperature: a constant temperature of about 40 °C, flow rate: 1.2 ml/min, detector: an ultraviolet absorption photometer (wavelength: 254 nm). The chromatographic conditions for saikosaponin b_2 were column: a stainless steel column packed with octadecylsilanized silica gel for liquid chromatography, mobile phase: a mixture of H_2O, MeOH and CH_3CN, column temperature: a constant temperature of about 50 °C, flow rate: 1.0 ml/min, detector: an ultraviolet absorption photometer (wavelength: 254 nm). The chromatographic conditions for ferulic acid were column: a stainless steel column packed with octylsilanized silica gel for liquid chromatography, mobile phase: a mixture of H_2O, CH_3CN and $(HCOO)_2$, column temperature: a constant temperature of about 25 °C, flow rate: 1.2 ml/min, detector: an ultraviolet absorption photometer(wavelength: 320 nm). Strict manufacturing processes and quality controls have satisfied Good Manufacturing Practices standards. Yokukansan has been approved by the Ministry of Health, Labour and Welfare as prescriptions covered under the National Health Insurance plan.

The three-dimensional high-performance liquid chromatography (3D-HPLC) profile of representative batches of yokukansan is shown in Fig. 1. For the analysis of components, the dried extract (1.0 g) of yokukansan was dissolved in 20 ml methanol under ultrasonication for 30 min and then centrifuged at 3000 rpm for 5 min. The supernatant was filtered through a 0.45-μm membrane and an aliquot of the filtrate was injected into a high-performance liquid chromatograph (Shimadzu SPD-M10AVP, Shimadzu Co., Kyoto, Japan). The chromatographic conditions were column: TSK-gel ODS-80TS (4.6ϕ mm × 250 mm long, Tosoh Co., Tokyo, Japan), mobile phase: a linear gradient with 0.05 M $AcONH_4$, pH 3.6 (90 → 0%) and 100% CH_3CN (10 → 100%) for 60 min, column temperature: 40 °C, flow rate: 1.0 ml/min, detector: diode array, and scan range: UV 200–400 nm. The compounds shown on the chromatogram were classified on the basis of the constituent herbs of yokukansan (Table 1).

Table 1
Classification of the compounds identified in the three-dimensional chromatogram according to.

Constituent herbs of yokukansan	Compounds
Atractylodis lanceae rhizome	4E,6E,12E-tetradecatriene-8,10-diyne-1,3,14-triol, 12-isovaleroyl-2E,8E,10E-triene-4,6-diyne-1,14-diol, 14-isovaleroyl-2E,8E,10E-triene-4,6-diyne-1,12-diol, atractylodinol, acetylatractylodinol, atractylodin
Cnidii rhizoma	Ferulic acid, ligustilide
Uncariae uncis cum ramulus	Geissoschizine methyl ether, hirsuteine, hirsutine
Angelicae radix (*Angelica acutiloba*)	Xanthotoxin, ligustilide
Bupleuri radix	Saikosaponin b1, saikosaponin b2
Glycyrrhizae radix	Formononetin, formononetin-7-*O*-glucoside, liquiritigenin, liquiritin, liquiritin apioside, glycyrrhizin, glycyroside, isoliquiritin apioside, isoliquiritin, isoliquiritigenin, glycycoumarin

An open label study design was used to examine the effects of yokukansan in patients with VaD. The present study was based on 13 patients who were diagnosed as having a VaD according to the diagnostic criteria of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) (Roman et al. 1993). All patients started 4-week course of yokukansan 2.5 g (1.08 g of extract) three times every day before meals.

The data were collected from the Research Institute for Brain and Blood vessels, Akita Prefectural Center of Rehabilitation and Psychiatric Medicine, and Iwate Medical University between January 2006 and March 2008. The ethical review committee of each institute approved this clinical study. Written informed consent was taken from the patients or their families before the study. All patients underwent a uniform evaluation including a medical history, and physical and neurological examination. The Mini-Mental State Examination (MMSE) was used for the assessment of cognitive function. The BPSD were evaluated using the Neuropsychiatric Inventory (NPI) (Cummings et al. 1994). As to 10 subcategories for NPI, such as delusion, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability and aberrant behavior, the frequency and severity were evaluated in 4 grades. The activity of daily living (ADL) was assessed by the Barthel Index (BI) (Mahoney and Barthel 1995) and Disability Assessment for Dementia (DAD) (Gelinas et al. 1999). Extrapyramidal signs and parkinsonism were evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) (Martinez-Martin et al. 1994). The inclusion criterion was that at least one subcategory for NPI was equal or greater than 4 points. Subjects were excluded from the study if any of the following criteria was met; (1) if they were suspected as other types of dementia including AD; (2) if they were taking traditional Japanese medicine other than yokuokansan; (3) their BPSD were suspected to be caused by drug use or metabolic intoxication; (4) if they were suspected to have neoplasma and acute