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

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ARTICLE INFO

Keywords:
Yokukansan
Behavioral and psychological symptoms of dementia
Vascular dementia

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.

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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-HFC, 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.

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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 (Angelicae acutiloba), 2 g of Bupleuri radix, 1.5 g of Glycyrrhizae radix, and 3 g of Uncariae uncis 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 b2 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 H2O, CH3CN and CH3COOH, 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 b2 were column: a stainless steel column packed with octadecylsilanized silica gel for liquid chromatography, mobile phase: a mixture of H2O, MeOH and CH3CN, 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 octadecylsilanized silica gel for liquid chromatography, mobile phase: a mixture of H2O, CH3CN 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 (4.6×250 mm) at 35 °C, mobile phase: a linear gradient with 0.05 M AConH2O, pH 3.6 (90→0%) and 100% CH3CN (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).

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 yokukansan; (3) their BPSD were suspected to be caused by drug use or metabolic intoxication; (4) if they were suspected to have neoplasma and acute

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

<table>
<thead>
<tr>
<th>Constituent herbs of yokukansan</th>
<th>Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atractylodis lanceae rhizome</td>
<td>4E,6E,12E-tetradecatriene-8,10-diyn-1,3,14-triol,</td>
</tr>
<tr>
<td></td>
<td>12-isovaleroyl-2E,6E,10E-triene-4,6-diyn-1,14-diol,</td>
</tr>
<tr>
<td></td>
<td>14-isovaleroyl-2E,6E,10E-triene-4,6-diyn-1,12-diol,</td>
</tr>
<tr>
<td></td>
<td>acetylactrycodiol, atracyxyldiol</td>
</tr>
<tr>
<td>Cnidii rhizoma</td>
<td>Ferulic acid, ligustilide</td>
</tr>
<tr>
<td>Uncariae uncis ramulus</td>
<td>Geissoschizine methyl ether, hisbuteine, hisbuteine</td>
</tr>
<tr>
<td>Angelicae radix (Angelica acutiloba)</td>
<td>Xanthotoxin, ligustilide</td>
</tr>
<tr>
<td>Bupleuri radix</td>
<td>Saikosaponin b1, saikosaponin b2</td>
</tr>
<tr>
<td>Glycyrrhizae radix</td>
<td>Formomononitin, formomononitin-7-O-glucoside,</td>
</tr>
<tr>
<td></td>
<td>liquiritigenin, liquiritin, liquiritin apoixide,</td>
</tr>
<tr>
<td></td>
<td>isoliquiritin apoixide, isoliquiritin, isoliquiritin,</td>
</tr>
<tr>
<td></td>
<td>glycycurmarin</td>
</tr>
</tbody>
</table>
inflammation. The subjects' mean age was 71.2 ± 6.5 years old. Nine men and 4 women were included in the present study. The elapsed time since the initial diagnosis of VaD was 2.2 years. All patients had hypertension. The demographic data of the patients are shown in Table 2.

The MMSE, NPI, BI, DAD and UPDRS were carried out repeatedly at the baseline and the end of study (4th week). Results were expressed as the mean ± SD. The statistical assessment of the treatment effects on each study variable was performed using non-parametric statistics. In all statistical analyses, p-values greater than 0.05 were considered to be significant.

Table 2
Demographical presentation of the subjects.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of BPSD (weeks)</th>
<th>MRI findings</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>Male</td>
<td>12</td>
<td>Infarction</td>
<td>HT, DM, DL ASO</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>Female</td>
<td>32</td>
<td>infarction</td>
<td>HT</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>Male</td>
<td>25</td>
<td>Infarction</td>
<td>HT, DM, ND</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>Male</td>
<td>22</td>
<td>Infarction</td>
<td>HT</td>
</tr>
<tr>
<td>5</td>
<td>77</td>
<td>Male</td>
<td>24</td>
<td>Infarction</td>
<td>AF, HT, CAD</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>Male</td>
<td>30</td>
<td>Infarction</td>
<td>DL, HUA</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>Male</td>
<td>20</td>
<td>Infarction</td>
<td>AF, HT</td>
</tr>
<tr>
<td>8</td>
<td>79</td>
<td>Female</td>
<td>79</td>
<td>Infarction</td>
<td>HT</td>
</tr>
<tr>
<td>9</td>
<td>76</td>
<td>Female</td>
<td>59</td>
<td>Infarction</td>
<td>CMP, HT, DL</td>
</tr>
<tr>
<td>10</td>
<td>66</td>
<td>Female</td>
<td>48</td>
<td>Infarction</td>
<td>AF, DM, ND</td>
</tr>
<tr>
<td>11</td>
<td>77</td>
<td>Male</td>
<td>34</td>
<td>Infarction</td>
<td>HT, DVT, ND</td>
</tr>
<tr>
<td>12</td>
<td>61</td>
<td>Male</td>
<td>23</td>
<td>Infarction</td>
<td>HT</td>
</tr>
<tr>
<td>13</td>
<td>80</td>
<td>Male</td>
<td>95</td>
<td>Infarction</td>
<td>HT, DL, ND</td>
</tr>
</tbody>
</table>

HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; ASO, arteriosclerosis obliterans; BD, neurogenic bladder; AF, atrial fibrillation; CAD, coronary artery disease; HUA, hyperuricacidemia; CMP, cardiomyopathy; DVT, deep vein thrombosis.

Results

The mean MMSE scores were 15.3 ± 8.5 and 15.8 ± 9.0 for the baseline and after the treatment, respectively. There was no significant difference before and after the treatment. The mean overall NPI score was 33.0 ± 17.3 at the baseline, and was 23.6 ± 13.9 after the treatment with yokukansan. The overall NPI score significantly decreased after the treatment (p < 0.05) (Fig. 2). In the subcategories for NPI, the mean subscores for agitation were 6.9 ± 4.2 and 4.1 ± 3.7 at the baseline and after the treatment, respectively. There was a significant improvement in the subcategory for agitation (p < 0.05). The mean subscores for disinhibition were 5.1 ± 2.2 and

Fig. 1. The three-dimensional HPLC profile of yokukansan.

Fig. 2. Comparison of the mean overall NPI scores before and after the treatment with yokukansan. *p < 0.05.
3.6 ± 2.2 at the baseline and after the treatment, respectively, and there was a significant improvement (p < 0.05). None of our VaD patient complained hallucination at the baseline or after the treatment (Fig. 3). The mean BI was 36.2 ± 31.9 at the baseline and was 40.8 ± 30.3 after the treatment, and there was no significant difference. The mean DAD was 20.5 ± 18.9 at the baseline and was 24.6 ± 20.8 after the treatment, and there was no significant difference. The mean UPDRS was 17.2 ± 11.0 at the baseline and was 16.1 ± 10.9 after the treatment, and there was no significant difference.

Case 11 who had been diagnosed as having a deep vein thrombosis developed a pulmonary embolism on 11th day and was dropped out from the study. No other adverse event was reported in remaining 12 subjects during the study. There was no significant interval difference in the mean values for the complete blood cell count (CBC) or biochemistry including electrolytes.

### Discussion

The present results suggest that yokukansan will be beneficial in the treatment of BPSD in VaD patients, although the total number of the subjects was limited and an open label study design was employed this time. In addition, there was also a significant improvement in the subcategories of agitation and disinhibition which often increase burden of the family and caregivers. On the other hand, the mean MMSE scores did not differ significantly before and after the treatment with yokukansan during 4-week observation. Similar to the previous studies, the short-term changes in BPSD were not reflected on the mean MMSE score which mainly based on the memory function. There was a tendency toward the mean BI and DAD to be mildly improved after the treatment with yokukansan in our VaD patients. At least there was no deterioration in UPDRS which reflect the extrapyramidal symptoms and parkinsonism after the treatment with yokukansan. These results may indicate that yokukansan has beneficial effects on BPSD without causing adverse influence on the ADL and motor function in elderly patients with dementia.

Unlike AD patients, VaD patients frequently have motor deficits such as hemiparesis and ataxia because VaD is based on various stroke subtypes. Extrapyramidal signs (EPS) which are often induced by antipsychotics may deteriorate the ADL and motor function of VaD patients. As compared with other type of dementias, the indication of antipsychotics is often limited in VaD patients even when they show marked BPSD due to the possible EPS. Since yokukansan had beneficial effects on BPSD such as agitation and disinhibition without causing EPS in our VaD patients, yokukansan can be regarded as a promising drug for the treatment of BPSD in VaD patients.

Postmortem studies showed that cortical and subcortical 5-HT concentration was lower in AD patients with BPSD than in those without BPSD (Lai et al. 2003). A relationship between the 5-HT transporter and development of BPSD was demonstrated in AD patients (Assal et al. 2004; Pritchard et al. 2007). Polymorphism of the dopamine receptors genes was involved BPSD in AD patients (Sweet et al. 1998). An association was also shown between polymorphism of serotonin receptors genes and visual and auditory hallucinations (Holmes et al. 1998). Growing evidence has suggested a role for 5-HT in the development of BPSD.

Pharmacological treatment for BPSD is basically maintained by increasing the activity of acetylcholine, and/or by decreasing or modulating the activity of dopamine and serotonin. Conventional antipsychotics are known to share high affinity for the D2 dopamine receptor, whereas pharmacological profiles of atypical antipsychotics include relatively lower affinity for D2 dopamine receptors along with higher affinity for 5-HT2 and 5-HT3 receptors (Kapur et al. 1995, 2000). Recently, the balance between dopamine and serotonin systems has been drawing attention in the treatment of BPSD.

Yokukansan has been used for the treatment of insomnia, irritability and confusion for many years, and the pharmacological effects of yokukansan is thought to be associated with SHT receptors. In addition, recent report showed that yokukansan inhibited the head-twitch responses which were induced by 2,5-dimethoxy-4-iodoamphetamine (5-HT2A and 5-HT2C receptor agonist), and suppressed the expression of 5-HT2A receptors in the laboratory settings (Egashira et al. 2008). It has been demonstrated that yokukansan possesses 5-HT1A partial agonistic effect (Kanno et al. 2009; Terawaki et al. 2010) and inhibitory effect of glutamate-mediated excitotoxicity (Kawakami et al. 2009; Ikarashi et al. 2009). Yokukansan consists of several herbal ingredients: Atractylidis Lanceae rhizoma, Poria, Cnidii rhizoma, Angelicae Radix (Angelica acutiloba), Bupleuri Radix, Glycyrrhizae Radix and Uncariae Uncis Cum Ramulus. The alkaloids obtained from Uncariae Uncis Cum Ramulus were found to be partial agonists for 5-HT receptors (Kanatani et al. 1985). These pharmacological effects of yokukansan on the SHT receptors are considered to be beneficial in the treatment of BPSD including agitation and disinhibition.

There has been mounting evidences concerning the beneficial effects of yokukansan on BPSD in not only AD patients but also those with dementia with Lewy bodies (DLB) (Iwasaki et al. 2005; Mizukami et al. 2009). The present report will add a new evidence about the effects of yokukansan on BPSD in VaD patients. This may expand the pharmacological choice in the treatment of BPSD.

### Conclusion

Even though the number of subjects was limited and an open-label study design was used in our investigation, 4-week administration of yokukansan significantly improved BPSD including agitation and disinhibition without causing extrapyramidal adverse effect or deterioration of ADL in VaD patients. The present results suggest that yokukansan is beneficial for the treatment of BPSD in VaD patients.

### Disclosure statement

This study was financially supported by Tsumura & Co., the pharmaceutical company that provided yokukansan and the result of three-dimensional HPLC analysis.
Acknowledgement

Author contributions: Dr. Nagata prepared the manuscript, has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Yokoyama, Department of Rehabilitation Akita Prefectural Center of Rehabilitation and Psychiatric Medicine, Dr. Yamazaki, Dr. Takano and Dr. Maeda, Department of Neurology, Research Institute for Brain and Blood Vessels, and Dr. Takahashi and Dr. Terayama, Department of Neurology, Iwate Medical University were clinical investigators and contributed to the study conception, patient recruitment, reviewing of the data.

References


