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Effect of yokukansan on the behavioral and psychological symptoms of dementia in elderly patients with Alzheimer's disease

Akira Monji [a,*], Masashi Takita [b,1], Takaaki Samejima [c], Toshihiro Takaishi [c], Kazuhito Hashimoto [d], Hiroyuki Matsunaga [e], Mariko Oda [f], Yasuhisa Sumida [g], Yoshito Mizoguchi [a], Takahiro Kato [a], Hideki Horikawa [a], Shigenobu Kanba [a]

[a] Department of Neuropsychiatry, Graduate School of Medical Sciences, Kysushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
[b] Imazu Red Cross Hospital, 377 Imazu, Nishiku-ku, Fukuoka 819-0165, Japan
[c] Sameshima Hospital, 272 Osoekawa, Fujicho, Saga 840-0521, Japan
[d] Seiyu Hospital, 5457 Kawakubo, Kuboizumicho, Saga 849-0901, Japan
[e] Hayatsue Hospital, 827 Fukudomi, Kawasoe, Saga 840-2201, Japan
[f] Nakataku Hospital, 2512-24 Takubaru, Kitatakucho, Taku, Saga 846-0003, Japan
[g] Sumida Hospital, 1423 Amasumi, Wakamatsu-ku, Kitakyushu, Fukuoka 808-0122, Japan

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ABSTRACT

Objective: The aim of this study was to investigate the effects of yokukansan (YKS) on the behavioral and psychological symptoms of dementia (BPSD) in elderly patients with Alzheimer's disease (AD).
Methods: Fifteen patients with AD (mean age: 80.2±4.0 years) participated in the study. The Mini-Mental State Examination (MMSE) was used for the assessment of cognitive function. BPSD were evaluated using the Neuropsychiatric Inventory (NPI). The Barthel Index was used for the assessment for the activities of daily living (ADL). The treatment with YKS along with sulpiride, a dopamine D_2 selective antipsychotic, was performed for 12 weeks.
Results: Fourteen patients completed the trial. After the 12 weeks of treatment with YKS, significant improvement of the mean NPI score was observed while no significant improvement was observed in the control group. The average dose of sulpiride at the end of the present study was less in the YKS group than in the control group. The MMSE results did not change either in the YKS group or in the control group. The Barthel Index did not significantly change either in the YKS group or in the control group. No serious adverse effects were noted.
Conclusions: Twelve weeks of the YKS treatment significantly improved BPSD with less antipsychotics in elderly patients with AD. The YKS treatment did not cause any cognitive decline or ADL decline and no serious adverse effects were noted. The present study suggests that YKS is beneficial for the treatment of BPSD and that it can possibly reduce the doses of antipsychotics required for the treatment of BPSD. Further studies with larger patient populations using a double-blind placebo-controlled design should be performed.

1. Introduction

Patients with dementia experience progressive cognitive impairments such as memory deficits and impaired executive functioning. The behavioral and psychological symptoms of dementia (BPSD) are also commonly seen in patients with Alzheimer's disease (AD) and other types of dementia. It is estimated that 60–80% of patients with dementia have BPSD at any one time (Lawlor, 2002). Cognitive failure is not, in itself, a sufficient explanation for functional disability or impaired quality of life for people with dementia. BPSD often causes considerable caregiver stress and hastens institutionalization of patients with dementia. Relatives and caregivers are thus likely to identify BPSD as the most important features of dementia (McKeith and Cummings, 2005; Jeste et al., 2008). While there have been several studies of pharmacological interventions for BPSD, the strategy of treatment has not been sufficiently established. Pharmacological interventions including antipsychotics and acetylcholine esterase inhibitors (AchEI) have been investigated, but elderly patients with dementia are particularly sensitive to the adverse effects such as extrapyramidal symptoms and cognitive decline. Moreover, concerns have been recently expressed regarding an increased risk of cerebrovascular adverse events (CVAEs) in elderly patients with dementia treated with antipsychotics (Schneider et al., 2006; Rainer

Abbreviations: YKS, yokukansan; BPSD, behavioral and psychological symptoms of dementia; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; AD, Alzheimer's disease.

* Corresponding author. Fax: +81 92 642 5644.
E-mail address: amonji@hf.rim.or.jp (A. Monji).
[1] Present address: Takita Memory Mental Clinic, 5-13-8 Muromi, Sawaraku-ku, Fukuoka 814-0015, Japan.

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Table 1
The demographic data of the patients

Subjects(n)	YKS group 10	Control 5	Total 15	*P* Value
Age(mean±SD)	80.8±4.7	79.0±2.0	80.2±4.0	Wilcoxon test $p=0.175$
Sex(male/female)	2/8	0/5	2/13	Fisher excact test $p=0.524$
Body weight(mean±SD)	44.5±8.2	46.3±3.3	45.1±6.9	Wilcoxon test $p=0.582$
Complication (presence/absence)	5/5	4/1	9/6	Fisher excact test $p=0.580$
NPI(total)	26.7±15.7	22.4±12.8	25.3±14.5	Wilcoxon test $p=0.425$
Barthel Index	77.5±16.7	63.0±34.0	72.7±23.7	Wilcoxon test $p=0.620$
MMSE	15.1±4.0	16.4±3.5	15.5±38	Wilcoxon test $p=0.423$

et al., 2007; Jeste et al., 2008; Kuehn, 2008; Sultzer et al., 2008). Clinicians and caregivers are left with unclear choices in treatment of BPSD. A systematic review indicated that some herbs and herbal formations were useful for the treatment of cognitive impairments of AD (Dos Santos-Neto et al., 2006). Yi-Gan San (yokukansan in Japanese) was developed in 1555 by Xue Kai as a remedy for restlessness and agitation in children. A recent report suggests the involvement of the 5-HT system in the psychopharmacological effects of yokukansan (YKS) (Egashira et al., 2008). The clinical efficacy and safety of YKS for improvement of cognitive function, BPSD, and activities of daily living (ADL) have been reported (Iwasaki et al., 2005a,b; Shinno et al., 2007, 2008). These studies included patients with dementia other than AD. The aim of this study was to investigate the effects of YKS on BPSD in patients with AD. We also tested for the presence of adverse effects during YKS administration.

2. Methods

2.1. Subjects

The subjects were patients admitted to Kyushu University-affiliated Hospitals. The data were collected from January 2006 to March 2008. The diagnosis of dementia was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (American Psychiatric Association, 1994). The diagnosis of Alzheimer's disease was made according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria (McKhann et al., 1984). Each patient received 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). The Barthel Index, the higher scores of which indicate better performance, was used for the assessment for the ADL (Mahoney and Barthel, 1965). We included patients who satisfied the following criteria: (1) patients with AD at an age between 55 years and 85 years, (2) an MMSE score of ≥6 and ≤23 after the treatment with sulpiride 50 mg/day for 2 weeks, (3) presence of BPSD with a NPI score of ≥6 on at least 1 of the delusions, hallucinations, agitation/aggression, disinhibition, irritability/lability or aberrant motor activity subscales after the treatment with sulpiride 50 mg/day for 2 weeks, and (4) stable physical condition for at least the past year. The exclusion criteria were (1) treatment with Chinese herbal medicine other than YKS and psychotropic medication other than sulpiride, AchEI and anti-parkinsonism drugs, (2) other types of dementia, (3) delirium and amnesia due to drug use, metabolic intoxication or inflammation, (4) major physical illness such as neoplasma and acute inflammation that would likely prevent completion of the study. The Institutional Review Board of Kyushu University Hospital approved this study. All subjects gave informed consent according to the institutional guidelines and the recommendations of the Declaration of Helsinki.

2.2. Intervention and measurements

We included 15 patients who met the inclusion criteria in the present study. After a detailed explanation of the study, we obtained written informed consent from the participants and /or their families. At baseline, the MMSE and NPI were evaluated. All patients started to take sulpiride 50 mg/day. Sulpiride, which is a dopamine D_2 selective antipsychotic, is frequently used for the treatment of the BPSD in Japan although it is not a well-known antipsychotic outside Japan. After 2 weeks of sulpiride treatment (baseline), the MMSE, the NPI, and the Barthel Index were evaluated to select the patients with AD who did not favorably respond to sulpiride. According to the NPI scores at the baseline, 15 patients were included in the present study. These patients were randomly assigned to the YKS group ($N=10$) and the control group ($N=5$) using a random number table. The demographic data of the patients are shown in Table 1. One patient of the control group was excluded from the present study because of the emergence of severe peripheral edema. Ten patients of the YKS group received 2.5 g of YKS (1.5 g of extract) three times every day before meals for 12 weeks. All patients continued to take sulpiride 50 mg/day and were reassessed every 4 weeks by the NPI as well as the Barthel Index. The dose of sulpiride was changed according to the following criteria; (1) an NPI score of ≥8 on at least 1 of the delusions, hallucinations, agitation/aggression, disinhibition, irritability/lability or aberrant motor activity subscales resulted in an increase of the sulpiride dose of 50 mg/day (2) an NPI score of <4 on all of the above subscales: resulted in a decrease of the sulpiride dose of 50 mg/day. To examine the existence of adverse effects, we observed general conditions, including extrapyramidal signs and peripheral edema and hypokalemia. The laboratory data of all the patients were evaluated every 4 weeks.

2.3. Data analysis

The statistical assessment of the treatment effects on each study variable was performed using non-parametric statistics. In all of the analyses p-values <0.05 were considered to be significant. The data are presented as the mean±SD.

3. Results

After the 12 weeks of treatment with YKS, significant improvement of the mean NPI score was observed while no significant improvement was observed in the control group (Fig. 1). No significant improvement was observed in each subscale of the NPI. (data not shown) The average dose of sulpiride at the end of the present study tended to be less in the YKS group than in the control group ($p=0.141$). (Fig. 2). The MMSE results did not significantly change either in the

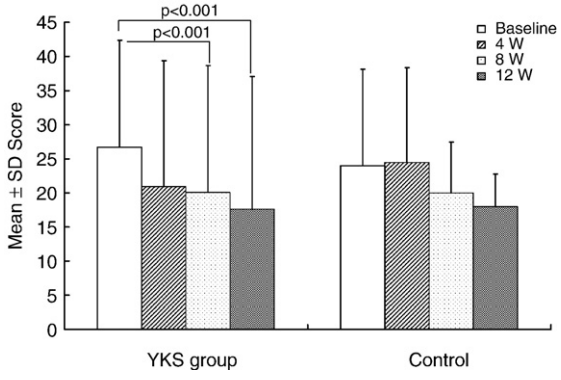

Fig. 1. The results of the neuropsychiatric inventory (NPI). After 12 weeks of treatment of YKS, significant improvement of the mean NPI score was observed while no significant improvement was observed in the control group. In all the analyses p-values <0.05 were considered to be significant. The data are presented as the mean±SD.