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ScienceDirect
Progress in Neuro-Psychopharmacology & Biological Psychiatry 32 (2008) 881–885
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

Effect of *Yi-Gan San* on psychiatric symptoms and sleep structure at patients with behavioral and psychological symptoms of dementia ☆

Hideto Shinno [a,b,*], Yasushi Inami [a,c], Takuji Inagaki [a], Yu Nakamura [b], Jun Horiguchi [a]

[a] *Department of Psychiatry, Shimane University Faculty of Medicine, 89-1 Enya, Izumo, Shimane 693-8501, Japan*
[b] *Department of Neuropsychiatry, Kagawa University School of Medicine, 1750-1 Ikenobe, Miki, Kita, Kagawa 761-0793, Japan*
[c] *Department of Psychiatry, Ehime Rosai Hospital, 13-27 Minami Komatsubara, Niihama, Ehime 792-8550, Japan*

Received 3 September 2007; received in revised form 26 November 2007; accepted 30 December 2007
Available online 11 January 2008

Abstract

Objective: Recently, traditional herbal medicines have been reported to be effective for behavioral and psychological symptoms of dementia (BPSD). This study aims to examine the efficacy of *Yi-Gan San* (YGS) in the improvement of BPSD and sleep disorders in patients with dementia.
Methods: Five patients (1 male and 4 female) with dementia in accordance with DSM-IV criteria were investigated. Participants were treated with YGS for 4 weeks. The Nursing Home version of Neuropsychiatric Inventory (NPI-NH) for the assessment of BPSD, the Mini-Mental State Examination (MMSE) for cognitive function, polysomnography for evaluation of sleep structure, and the Pittsburgh Sleep Quality Index for subjective sleep quality were carried out at baseline and at the end of treatment.
Results: All patients completed the trial. Significant improvements in the total NPI-NH score (34.0±6.5 to 12.8±6.6) as well as delusions, hallucinations, agitation/aggression, anxiety, and irritability/lability, whereas MMSE scores were unchanged. PSG revealed increases in total sleep time, sleep efficiency, stage 2 sleep, and decreases in the number of arousals and periodic limb movements. Subjective sleep quality was also improved. No adverse effects were observed.
Conclusion: YGS was effective for BPSD and sleep disturbances, and well tolerated in patients with dementia. Further examinations using a double-blind placebo-controlled design are necessary.

Keywords: Herbal medicine; Neuropsychiatric Inventory; Periodic limb movements; Pittsburgh Sleep Quality Index; Polysomnography

1. Introduction

Patients with dementia experience progressive cognitive impairments such as memory deficits and impaired executive functioning. Behavioral and psychological symptoms of dementia (BPSD) are also commonly seen in patients with Alzheimer's disease (AD) (Flint, 1991; Paulsen et al., 2000), dementia with Lewy bodies (DLB) (Ballard et al., 1999), and other types of dementia (O'Brien, 2003). BPSD is a significant burden to caregivers (Onishi et al., 2005) and often relates to poor performance on activities of daily living (ADL) (Norton et al., 2001). While there have been several studies of pharmacological interventions for BPSD, the strategy of treatment has not been sufficiently established. The current available medications for the treatment of BPSD present some limitations such as adverse effects. In this decade, traditional herbal medicine products have been used for the treatment in AD and other types of dementia. A systematic review (dos Santos-Neto et al., 2006) indicated that some herbs and herbal formations including Yi-Gan San (YGS,

Abbreviations: BPSD, Behavioral and psychological symptoms of dementia; DLB, Dementia with Lewy Bodies; 5-HT, serotonin; GABA, γ-aminobutyric acid; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PLMs, periodic limb movement during sleep; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; YGS, *Yi-Gan San.*

☆ This study was conducted at Department of Psychiatry, Shimane University Faculty of Medicine.

* Corresponding author. Department of Neuropsychiatry, Kagawa University School of Medicine, 1750-1 Ikenobe, Miki, Kita, Kagawa 761-0793, Japan. Tel.: +81 87 891 2165; fax: +81 87 891 2168.
E-mail address: shinnoh@med.kagawa-u.ac.jp (H. Shinno).

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doi:10.1016/j.pnpbp.2007.12.027

Yokukan-San in Japanese, *Pulvis depressionis efficientiae*) were useful for cognitive impairment of AD. The clinical efficacy and safety of YGS for improvement of cognitive function, BPSD, and activities of daily living have been investigated (Iwasaki et al., 2005a).

Previous studies of sleep in demented patients have revealed a decrease in the amount of slow wave sleep (Prinz et al., 1982) and rapid eye movement (REM) sleep (Satlin et al., 1991), reduction of nocturnal melatonin secretion (Waldhauser et al., 1984), and advancement of the sleep phase (Czeisler et al., 1992). In addition, periodic limb movements during sleep (PLMs) are commonly observed in the elderly and often cause the sleep disturbances. PLMs are generally considered to produce poor sleep quality by provoking electroencephalogical arousal or awakening (Bastuji and García-Larrea, 1999).

However, there have been few polysomnographic studies investigating prospectively on the effect of drugs prescribed for BPSD. The effects of herbal medicine on the sleep disturbances and the disturbed polysomnographical findings have not sufficiently understood, although there is a case report (Shinno et al., 2007).

The aim of this study was to investigate the effects of YGS on both BPSD and sleep structure in patients with dementia. We also tested for the presence of adverse effects during YGS administration.

2. Methods

2.1. Subjects

The subjects were patients who visited the Memory Clinic at Shimane University Hospital. Data were collected from September 2006 to March 2007. The diagnosis of dementia was made according to *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 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), and the diagnosis of dementia with Lewy bodies (DLB) was made according to criteria described by the Consortium on DLB (McKeith et al., 1996; McKeith et al., 2005).

Each patient received a uniform evaluation including a medical history, physical, and neurological examination. The Mini-Mental State Examination (MMSE) was carried out for assessment of cognitive function. BPSD were evaluated using the Neuropsychiatric Inventory-Nursing Home version (NPI-NH) (Wood et al., 2000). Head magnetic resonance imaging (MRI), and single photon emission computer tomography (SPECT) were also carried out.

We included patients who satisfied the following criteria: (1) patients with AD or DLB, (2) an MMSE score of <24, (3) presence of BPSD, and (4) stable physical condition for at least the past year. The exclusion criteria were (1) treatment with neuroleptics, cholinesterase inhibitors, or YGS at baseline, (2) delirium, (3) major physical illness that would be likely to prevent completion of the study.

The institutional review board of Shimane University School of Medicine approved this study. All subjects gave informed consent according to institutional guidelines and the recommendations of the Declaration of Helsinki.

2.2. Intervention and measurements

Ten patients who met the inclusion criteria visited our Memory Clinic. Five subjects were excluded according to the exclusion criteria. Two patients had been administrated with neuroleptics (risperidone, quetiapine), and one patient with YGS. There was one patient who exhibited delirium, and one patient was found to have leukemia. Five patients (1 male/4 female) who met the criteria described above participated in this study. After a detailed explanation of the study, we obtained written informed consent from participants and/or their families.

At baseline, the MMSE and NPI-NH were evaluated. These examinations were conducted on all subjects at 14:00 on the examination days. Baseline polysomnography (PSG) was carried out following the adaptation night. We performed overnight PSG by means of standard procedures that included recording a sleep electroencephalogram (C3–A2, C4–A1), bilateral eye movements, submental electromyography (EMG), bilateral tibialis anterior EMG, and an electrocardiogram. Sleep stage was scored according to standard criteria (Rechtschaffen and Kales, 1968). Sleep efficiency and the lengths of stage 1, stage 2, stage 3, stage 4, and stage REM sleep were obtained independently. Periodic limb movements during sleep (PLMs) were also estimated. The subjective sleep quality was also determined by the Pittsburgh Sleep Quality Index (Buysse et al., 1989) at baseline and after YGS administration.

After the baseline examinations, 2.5 g of YGS was administered before meals three times every day. All patients were reassessed 4 weeks later by means of NPI-NH and PSG. To examine whether adverse effects, we observed general conditions, including vital signs, every day. Laboratory data of all patients were evaluated at baseline and after YGS treatment. We used the Drug-induced Extrapyramidal Sign Scale (DIEPSS) (Inada et al., 2003) to examine whether YGS-induced extrapyramidal signs were presented. The DIEPSS is composed of eight individual parameters and one global assessment to measure EPS on 5-point scales.

2.3. Data analysis

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

3. Results

Five patients (1 male and 4 female) completed this study. The mean age was 81.6±6.9. Two patients were diagnosed with AD and three patients with DLB. Demographics and baseline characteristics of the five patients are shown in Table 1.