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Effect of Yokukansan, a Traditional Herbal Prescription, on Sleep Disturbances in Patients with Alzheimer's Disease

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Abstract

Objective: Evidence of the effects of Yokukansan (YKS), a traditional herbal medicine, on behavioral and psychological symptoms of dementia (BPSD) has accumulated. As well as BPSD, patients with Alzheimer's disease (AD) demonstrate poorer sleep quality. Specific sleep disorders such as sleep-disordered breathing and periodic limb movement disorder (PLMD) can be prevalent in the elderly. PLMs are generally considered to produce sleep fragmentation by provoking arousals. This study aimed to examine whether YKS alters polysomnography variables in patients with AD.

Methods: Seven patients (3 men and 4 women) with probable AD according to the standard criteria were investigated. Participants were treated with YKS for 4 weeks. The Neuropsychiatric Inventory for the assessment of BPSD, the Mini-Mental State Examination (MMSE) for cognitive function, polysomnography for evaluation of sleep structure and Pittsburgh Sleep Quality Index (PSQI) for subjective sleep quality, and Epworth Sleepiness Scale (ESS) were carried out at baseline and at the end of the treatment. The local institutional review boards approved this study. All patients gave written consent according to institutional guidelines and the tenets of the Declaration of Helsinki.

Results: Treatment with YKS resulted in a decreased NPI score, a prolonged total sleep time, a shortened sleep latency, an increased sleep efficiency, and decreased periodic limb movement during sleep. YKS also improved subjective evaluations with PSQI and ESS.

Conclusions: YKS was effective for BPSD and sleep disturbances in patients with AD. YKS did not induce daytime somnolence, extrapyramidal signs, or an increased apnea-hypopnea index.

Keywords: Alzheimer's disease; Behavioral and psychological symptoms of dementia (BPSD); Fragmentation of sleep; Herbal medicine; Neuropsychiatric inventory; Polysomnography; Periodic limb movement; Pittsburg sleep quality index

Abbreviations: BPSD: Behavioral and Psychological Symptoms of Dementia; 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; YKS: Yokukansan

Introduction

In patients with dementia, progressive cognitive impairments such as memory deficits and impaired executive functioning are presented. Behavioral and psychological symptoms of dementia (BPSD) are also commonly seen in patients with Alzheimer's disease (AD), diffuse Lewy body disease, and other types of dementia. BPSD are a significant burden to caregivers and often relate to poor performance in activities of daily living (ADL). While there are several studies on the pharmacological interventions in BPSD, the effects of therapeutic drugs on BPSD are not sufficiently understood. Traditional herbal medicines have been used with safety and efficacy. In this decade, the clinical efficacy and safety of Yokukansan (YKS) in cognitive function, BPSD, and ADL have been investigated [1]. YKS contains herbal medicines (Atractylodis Lanceae rhizona, Hoelen, Cnidii rhizoma, Angelicae radix, Bupleuri radix, Glycyrrhizae radix and Uncariae ramulus et uncus). Angelicae radix, an important herb in YKS, has been reported to have effects on γ-aminobutyric acid (GABA) and serotonin (5-HT) receptors [2].

Previous studies on sleep in the dementia patients have revealed decreases in amounts of slow-wave sleep [3] and rapid eye movement (REM) sleep [4], a reduction in the nocturnal secretion of melatonin [5], and advances of sleep phase [6]. In addition, increases in apnea-hypopnea and periodic limb movement during sleep (PLMS) are commonly observed in the elderly and often cause the sleep disturbance. PLMS is generally considered to produce poor sleep quality by provoking electroencephalogical arousals or awakenings [7,8]. PLMD is defined as a periodic limb movement (PLM) index of 15 or greater that is associated with an otherwise unexplained sleep-wake complaint. These changes result in sleep fragmentation and poorer sleep quality, and may contribute to sleep disturbances in the elderly. Because these features are noticeable in patients with AD, they are troubled by sleep disturbances in addition to BPSD [3,9]. The prevalence of sleep disturbance in AD has been estimated to be 25% in mild to moderate cases, and about 50% in moderate to severe cases [9]. Sleep problems in AD may be caused by a disrupted rhythm of melatonin production, a greater prevalence of obstructive sleep apnea syndrome, and modified sleep architecture [3]. Changes in sleep architecture in patients with AD

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seem to be an exaggeration of those that appear normally with aging. Previous studies using polysomnography (PSG) demonstrated that AD patients showed an increased frequency and duration of awakening, an increased proportion of stage I, and a reduced proportion of REM sleep and SWS when compared to elderly control subjects [3,10]. Due to these symptoms, patients with AD nap excessively in the daytime, have difficulty falling asleep at night, exhibit frequent nocturnal awakening, and wake up too early. Therefore, reducing sleep fragmentation and poor sleep efficiency would be beneficial for restoring their sleep quality.

There have, however, been very few polysomnographic studies on the effect of drugs prescribed for BPSD treatment in patients with dementia. This is particularly the case for traditional herbal prescriptions, although a preliminary study and case reports exist [11,12].

The aim of this study was to investigate the effects of YGS on both the BPSD and sleep structure in patients with dementia. We also observed whether any adverse effects were elicited during YKS administration.

Methods

Subjects

This study had a prospective, open-labeled design to assess the therapeutic effects of YKS. Data were collected between January 2009 and December 2014. We included patients admitted for the purpose of diagnosis and treatment for cognitive impairment. The diagnosis of probable AD was made according to the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) [13]. After being diagnosed, patients and their families were informed of the diagnosis.

We included patients who satisfied the following criteria: (1) they met criteria for probable AD, (2) they were over 70 years old, regardless of gender, (3) subjective sleep complaints were present, and (4) their physical condition had been stable for the past year. The exclusion criteria were: (1) taking neuroleptics, cholinesterase inhibitors, or YKS treatment at baseline, (2) they had medical illnesses that affected sleep quality or daytime alertness, (3) they met criteria for any other psychiatric disorders such as schizophrenia, mood disorders, or delirium, and (4) they had major physical illness that would be likely to prevent completion of the study.

The institutional review boards approved this study. All patients and responsible family members provided written consent according to institutional guidelines and the recommendations of the Declaration of Helsinki.

Evaluations and measurements at the baseline

Experienced, research-trained clinicians conducted semi-structured interviews with the subjects including a medical and psychiatric history, medication, aphasia battery, and neurological examination. Caregivers and/or next-of-kin were also interviewed. After a detailed explanation of the study, we obtained written informed consent from the subjects and their families.

Diagnosis: The diagnosis of probable AD was made according to the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) [13]. After being diagnosed, patients and their families were informed of the diagnosis.

MRI and technetium-99m ethyl cysteinate dimer (Tc-^{99m}-ECD) single photon emission computed tomography (SPECT) were also carried out as supplementary diagnostic methods.

Cognitive function and psychiatric symptoms: In all subjects, cognitive function was assessed with the Mini-mental State Examination (MMSE) [14]. The Clinical Dementia Rating (CDR) was used to determine whether or not dementia was present [15]. BPSD were evaluated using a Neuropsychiatric Inventory (NPI) score [16]. We adopted a 10-item NPI that does not include subscales on sleep disturbance for the following reasons: 1) Patients and their principal caregivers do not always share a room at night, and it is difficult to observe their nocturnal status. 2) We adopted PSG and a subjective rating tool for evaluating sleep. The 10-item NPI was used in the present study. This allowed us to avoid overlapping, and to evaluate BPSD in isolation. Subjective sleep quality and daytime somnolence were assessed with the Pittsburgh Sleep Quality Index (PSQI) [17], and Epworth Sleepiness Scale (ESS) [18], respectively. These examinations were carried out at 14:00 on the examination days.

Polysomnography (PSG): PSG was carried out following the adaptation night. Electrodes for the polysomnogram were attached until 16:30. We performed overnight PSG by standard procedures that included recording sleep electroencephalograms (C3-A2, C4-A1), bilateral eye movements, submental electromyography (EMG), an electrocardiogram, pulse oximetry, bilateral tibialis anterior EMG, nasal air flow by a pressure sensor, as well as rib cage and abdominal excursions. The sleep stage was scored according to standard criteria [19]. The total sleep time, sleep efficiency, and lengths of stages I, II, III, IV, REM were obtained. Stage III plus stage IV were calculated as SWS. REM sleep was defined and analyzed according to the scoring criteria of Lapierre and Montplaisir [20]. If the activities recorded on the tibialis anterior EMG meet the following criteria, we considered the as significant limb movements (LMs) [21]: i) The duration of an LM event is 0.5-10 seconds, ii) The minimum amplitude of a LM event is an 8 μV-increase in EMG voltage above resting EMG, iii) The timing of the onset of an LM event is defined as the point at which there is an 8 μV-increase in EMG voltage above resting EMG, and iv) The time LM event ended is defined as the start of a period lasting at least 0.5 seconds during which the EMG does not exceed 2 μV above resting EMG. To define a PLM series, the following rules were adopted [21]: i) The number of consecutive LM events is ≥ 4 LMs, ii) The period length between LMs to include them as part of a PLM series is 5-90 seconds, and iii) LM on 2 different legs separated by less than 5 seconds between movement onsets are counted as a single LM. The PLMS index was calculated as the number of PLMS/ total sleep time (hours). We scored apnea when all of the following criteria are met [21]; i) There is a drop in the peak thermal sensor excursion by> 90% of baseline, ii) The duration of the event lasts at least 10 seconds, iii) At least 90% of the event's duration meets the amplitude reduction criteria for apnea. We score hypopnea, if all of the following criteria are met [21]; i) The nasal pressure signal excursions drop by≧30% of baseline, ii) The duration of this drop occurs for a period lasts at least 10 seconds, iii) There is a≧4% desaturation from pre-event baseline, and iv) At least 90% of the event's duration must meet the amplitude reduction criteria for hypopnea. We scored arousal during sleep stages [21], if there is an abrupt shift of EEG frequency including *alpha, theta* and/or frequencies greater than 16 Hz (but not spindles) that lasted at least 3 seconds of stable sleep preceding the change. We scored arousal during REM sleep, when a concurrent increase in submental EMG lasted at least 1 second [21].

Intervention and outcome measurements

After the baseline examinations, 2.5 g of YKS were administered

before meals, three times every day. All patients were reassessed 4 weeks later by means of the NPI, the PSG, the PSQI, and the ESS. To examine whether adverse effects, including extrapyramidal signs, were present, we examined patients carefully and the extrapyramidal signs were evaluated with the Drug-induced Extrapyramidal Sign Scale (DIEPSS) [22].

These study variables were compared between baseline and after treatment with YKS.

Data analysis

Statistical assessment of the treatment effects on each study variable was performed using a Wilcoxon's signed rank test. Calculation was carried out with the software PASW Statistics 18.0™. When the *p*-value was less than 0.05, we considered the difference to be significant.

Results

Fifteen patients who met the criteria visited our Department. Eight patients were excluded according to the exclusion criteria. Five patients had been administered with neuroleptics, and 2 patients with YKS. One patient was found to have cancer.

Seven patients (3 males and 4 females) completed the study. The mean age was 78.7 ± 2.4 years old. Demographics and baseline characteristics of five patients are shown in Table 1.

The effect of YKS on the PSG variables and subjective sleep quality

The PSG variables are indicated in Table 2. When the PSG data at the baseline were compared with those obtained after YKS treatment, significant improvements were observed in total sleep time (p=0.02), sleep efficiency (p=0.02), stage II non-REM sleep (p=0.03), number of awakenings (p=0.02), the PLMs index (p=0.02), and wake after sleep onset (WASO) (p=0.02). YKS did not increase AHI (p=0.12). There were no subjects who presented REM sleep without atonia.

PSQI was carried to assess the subjective sleep quality. Higher scores indicate more severe complaints and a greater decrease in sleep quality. The mean PSQI scores were 10.9 ± 2.3 and 6.9 ± 1.1 at baseline and the after treatment, respectively (p=0.02). YKS thus improved subjective sleep quality. The mean ESS scores were 10.7 ± 1.8 and 6.7 ± 1.0 at baseline and after treatment, respectively (p=0.02). YKS also reduced daytime somnolence.

The effects of YKS on BPSD and cognitive function

The mean basal NPI score was 28.4 ± 4.6. After YKS treatment, a significant decrease in the score for NPI was observed, and the mean NPI score after four weeks of administration was 13.0 ± 4.1 (vs. baseline: p=0.018). The scores of total NPI and the subscales are indicated in Table 3. We observed significant decreases in subscale scores of delusions (p=0.016), hallucinations (p=0.014), agitation/aggression (p=0.017), anxiety (p=0.024) and irritability/lability (p=0.027).

Female/male	4/3	
	Mean ±Std. Dev.	Range
Age (years old)	78.1 ± 2.4	[76-83]
Education (years)	10.9 ± 1.4	[9-13]
MMSE	22.6 ± 3.4	[16-27]
Total NPI	28.4 ± 4.6	[19-33]
PSQI	10.9 ± 2.3	[7-14]
ESS	10.7 ± 1.8	[8-13]

Values represent the mean ± standard deviation [range]. Abbreviations: MMSE: Mini-Mental State Examination, NPI: Neuropsychiatric Inventory, PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale.

Table 1: The demography and clinical characteristics of subjects.

	Baseline	Treated with YKS	p value
Total sleep time (TST), min	237.3 ± 56.7	305.7 ± 51.1	0.02*
Sleep efficiency, %	52.7 ± 12.6	67.9 ± 11.4	0.02*
Sleep latency (min)	86.9 ± 42.8	36.3 ± 20.4	0.03*
Stage 1, % of TST	51.9 ± 5.5	35.0 ± 6.3	0.02*
Stage 2, % of TST	39.7 ± 3.4	51.9 ± 8.1	0.03*
Stage 3+4, % of TST	1.2 ± 1.8	2.2 ± 1.7	0.09
Stage REM, % of TST	7.2 ± 2.2	10.8 ± 4.2	0.06
No. of awakenings (n./hr)	13.7 ± 3.4	7.7 ± 2.4	0.02*
WASO (min)	212.7 ± 56.7	144.3 ± 51.1	0.02*
PLMS index (n./hr)	32.3 ± 9.0	20.5 ± 5.5	0.02*
apnea-hypopnea index (/hr)	9.8 ± 4.2	8.4 ± 2.6	0.12

Table 2: Effect of YKS on the polysomnography data.

	Baseline	Treated with YKS
Delusions	5.6 ± 1.6	1.9 ± 0.7
Hallucinations	3.9 ± 2.1	2.1 ± 1.9
Agitation/ agression	3.4 ± 1.8	1.1 ± 0.9
Depression/ dysphoria	1.6 ± 1.7	0.6 ± 0.8
Anxiety	2.9 ± 1.1	1.6 ± 1.1
Elation/ euphoria	0.3 ± 0.5	0.1 ± 0.4
Apathy/ indifference	3.1 ± 1.9	2.3 ± 1.5
Disinhibition	1.7 ± 1.6	0.9 ± 0.9
Irritability/ lability	4.0 ± 1.5	1.6 ± 0.8
Abberant motor activity	2.1 ± 1.9	1.0 ± 0.8
Total	28.4 ± 4.6	13.0 ± 4.1

All subjects received YKS for 4 weeks, and BPSD was evaluated by the Neuropsychiatric Inventory (NPI) at the end of each 4-week period. The values under the NPI represent frequency x severity scores. Data are presented as mean±SD. *P<0.05; basal vs. treated with YKS (a Wilcoxon's signed rank test)

Table 3: Effect of YKS on behavioral and psychological symptoms of dementia (BPSD).

The mean basal MMSE score was 17.9 ± 3.6. The mean MMSE score after four weeks of administration was 18.1 ± 2.8 (p=0.41). YKS administration did not disturb daytime cognitive function.

Observations of adverse effects

Treated with YKS, no adverse effects (including extrapyramidal signs) or significant changes in laboratory data were presented.

Discussion

YKS was developed as a remedy for restless and agitation. In this decade, there have been several case reports suggesting a therapeutic effect of YKS on BPSD. Iwasaki et al. reported a randomized, observer-blinded, controlled trial of YKS, and demonstrated that YKS was effective for BPSD and activities of daily living in dementia patients [1]. Several studies have confirmed the therapeutical effects on BPSD [11,23-26].

Sleep changes in patients with dementia seem to be an exaggeration of changes that appear normally with aging. Patients with AD have been reported to show an increased number and duration of awakenings, an increased percentage of stage I sleep, and a reduced percentage of slow wave sleep compared with elderly control subjects [3]. Moreover, increases in apnea-hypopnea index and PLMS index induce fragmentation of sleep. Patients with dementia such as AD usually complain of prolonged waking episodes after sleep onset. PLMS is

characterized by periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep, and is associated with an otherwise unexplained sleep-wake complaint [27]. PLMS are common, especially in the elderly, but the frequency may be clinically significant. Because these movements are associated with a partial arousal or awakening, higher PLMS indices lead to frequent sleep disruption. Although the precise mechanisms responsible for PLMS remain to be elucidated, the dopamine system is currently considered to be involved in the pathophysiology [28]. PLMS are most manifest in disorders involving hypofunction of the dopamine system [27,28], and dopamine receptor agonists decrease PLMS in patients with restless legs syndrome [29]. Administration of neuroleptics, potent dopamine D2 antagonists, or γ-hydroxybutyrate, which decreases dopamine release, lead to increases in PLMS [28]. Neuroimaging studies demonstrated that patients with a high PLMS index exhibited a decreased number of D2 receptor binding sites in the striatum, which was restored by dopamine replacement therapy [30]. Benzodiazepines and anticonvulsants are known to be effective for reducing PLMS, which may suggest that an alteration in the GABAergic as well as the dopaminergic system may be involved with PLMS. Angelicae radix, an important component of YKS, is known to affect dopamine, GABA, and serotonin receptors [2]. In aged rats, YKS has been reported to improve the decreased level of dopamine in the prefrontal cortex [31]. YKS has been reported to ameliorate age-related impairments of working memory via the dopaminergic system [32]. Therefore, YKS may be effective for restoring the dopaminergic and GABAergic neuronal function that are responsible for the increased PLMS.

Growing evidence suggests a role of 5-HT in BPSD. Postmortem studies have shown that cortical and subcortical 5-HT levels in patients of Alzheimer's disease with psychosis were lower than in those patients without psychosis [33]. Polymorphisms within 5-HT receptor, 5-HT2A and 5-HT2C, have been reported to relate with the development of BPSD in Alzheimer's disease [34]. We therefore consider that the effect of YKS on the serotonergic system may be of benefit in BPSD treatment. As for the relationship between 5-HT and PSG findings, atypical neuroleptics including olanzapine, which have a high affinity for 5-HT2A receptor, have been demonstrated to increase total sleep time and stage II sleep, while haloperidol, which has a less potent affinity for 5-HT2A receptor, did not affect stage II sleep. We think that the serotonergic effect of YGS may be beneficial for the treatment of BPSD and sleep disturbance. YGS is considered to be effective for treating the altered sleep structure that is commonly observed in patients with dementia.

In this study, YKS was demonstrated to improve subjective sleep quality and some PSG variables, as well as BPSD. These variables were total sleep time, sleep efficiency, sleep latency, percent of stage II sleep, number of awakenings and PLMS index. We may conclude that YKS reduces fragmentation of sleep in patients with AD. The effects on dopamine, 5-HT, and GABA are considered to be beneficial.

Conclusion

YKS is effective for reducing fragmentation of sleep. We speculate that the actions on the serotonergic, dopaminergic, and GABA ergic system might account for some of the therapeutic effects of YKS presented in this report.

Limitations and Future Directions

The major limitation was that this study was an open-labelled study with a small sample size. Accumulation of PSG data in more AD patients and randomized trials are necessary.

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