Yokukansan treatment of chronic renal failure patients receiving hemodialysis, with behavioral and psychological symptoms of dementia: An open-label study

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Introduction

Individuals with end-stage chronic renal failure (CRF) have 2- to 7- fold higher prevalence of cognitive impairment and dementia compared with the general population (1). Moreover, the frequency of cognitive impairment of patients undergoing hemodialysis is significantly higher than the general population, with cognitive impairment thought to be an independent predictor of mortality in dialysis patients (2). Behavioral and psychological symptoms of dementia (BPSD) are a significant burden to caregivers, and often relate to poor performance on activities of daily living (ADL), but despite this a strategy to treat BPSD has not been successfully established. Treating BPSD in CRF patients by using neuroleptics is often complicated because hemodialysis decreases the plasma concentration of neuroleptics by 20-25%, thereby inhibiting the affectivity of the drug. The time required for neuroleptics to reach steady state is also lengthened when compared to results seen in normal cases. Urinary potassium excretion is significantly decreased in CRF patients, therefore hyperkalemia is a common and critical problem in this subset of people (3). Excessive potassium must be removed by hemodialysis so hyperkalemia in CRF patients can be avoided, and some CRF patients require cation exchange resins, in addition to hemodialysis, to facilitate intestinal excretion of potassium despite the serious side effects (4).

Yokukansan (YKS) is an herbal medicine, which was developed as a remedy for restlessness and agitation in children. Several clinical studies have revealed the efficacy of YKS for BPSD with Lewy bodies (5), borderline personality disorders, tardive dyskinesia of schizophrenia, and sleep disturbance. The main adverse reaction of YKS is hypokalemia. Conversely, YKS might be an ideal alternative to the above-mentioned potassium-removing agents in the CRF patient.

The authors evaluated the efficacy and safety of YKS for CRF patients receiving hemodialysis with BPSD. Our clinical study suggested that YKS was effective and safe for BPSD in hemodialysis patients.

Methods

Subjects

Subjects were recruited after a preliminary psychiatric interview and further assessment in Yoshida General Hospital, Kurayoshi Hospital, Miyoshi Clinic, Hiroshima, Japan. All subjects were required to be diagnosed with CRF and receiving hemodialysis 3 times a week. Inclusion criteria were as follows; less than 20 points on the Mini-Mental State Examination, or diagnosis of dementia according to a structured clinical interview using the DSM-IV criteria. Patients with major medical or neurological illness were excluded. The local Institutional Review Board approved this study. Before being recruited, participants gave their written, informed consent.

Procedure

Prior to YKS treatment, all patients were assessed for age, past history, family history, name and dose of antipsychotics already administered. After assessment, 7.5 g of YKS powder was added to ongoing therapy with antipsychotics. Participants were asked about adverse events, side effects, and medication compliance every week. Neuropsychiatric Inventory (NPI) criteria before and after 4-week YKS treatment were compared. ADL of participants were evaluated using the Bathel index. Rating scale scores were confirmed by an independent researcher. Participants were assessed by field researchers.

Statistical analysis

Parametric data are reported as mean SD. The Wilcoxon signed-ranks test was used to compare mean differences in parametric data at baseline and at week 4. A probability value of less than 0.05 was considered statistically significant. Statistical analysis of data was carried out using Statcel (2nd edition) on Excel for Windows.

Safety assessments

Medical and disease history, physical examination, body weight, blood pressure, and electrocardiograms were assessed at baseline. Laboratory studies included a baseline screening for liver disease, metabolic dysfunction, electrolyte imbalance, anemia, adequate blood cell and platelet count, and presence of illegal drugs. A medical review was performed, together with assessment of body weight and blood pressure and a review of adverse events and concomitant medications at the end of the trial.

Results

A total of 12 patients were recruited for the present trial. A 79-year-old male patient who satisfied the diagnostic criteria of Alzheimer's dementia dropped out from the study, because he and his family preferred to use quetiapine a week after the initiation of YKS treatment. He continued to take YKS 7.5 g/day and quetiapine 50-100 mg/day together for 4 weeks and did not experience any adverse reactions.

The other 11 patients completed the 4-week observation period (Table 1). Analysis of the mean score for NPI scale revealed a significant improvement during the period of YKS administration (25.3 17.6 vs 8.36 4.46; p = 0.0069; Figure 1). Delusions and feelings of agitation were significantly improved (Figure 2). The mean score for the Bathel index showed no significant difference during the period of YKS administration (47.6 21.2 vs 50.4 22.1; p = 0.1441).

Laboratory parameters were within the range at baseline and remained in the reference range for the whole sample throughout the 4-week trial. Mean level of serum potassium was 3.89 0.56 mEq/l at baseline and 3.78 0.46 mEq/l at week 4, which was still within the normal range (Figure 2). Subjects reported a few mild and transient adverse events, including nausea (1 case) and tiredness (1 case), however, no subjects had severe adverse reactions necessitating discontinuation from the study.

Table 1: Demographics and clinical characteristics of 11 subjects diagnosed with dementia receiving hemodialysis prior to Yokukansan treatment

Age, mean ± SD, *years*		68.0 ± 7.3
Sex, N	male	7
	female	4
Diagnosis, N	AD	8
	VD	3
MMSE score		10.5 ± 6.0
Anti-psychotic use		
	haloperidole, N	6
	risperidone, N	3
	quetiapine, N	2
	perospirone, N	1
Number of antipsychotics, mean ± SD, N		1.18 ± 0.72
Dose of antipsychotic‡, mean ± SD, *mg/day*		164.2 ± 152.4

AD; Alzheimer's disease, VD; vascular dementia, MMSE; Mini-Mental State Examination, ‡; chlorpromazine equivalent

Figure1; Comparison of NPI, serum K concentration before and after YKS treatment (N=11)

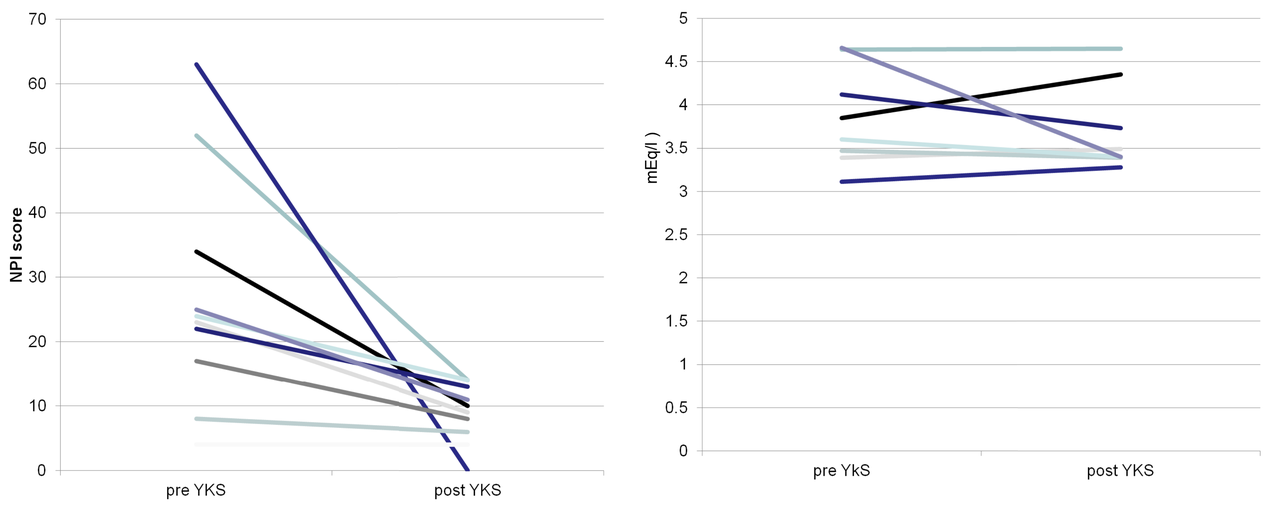
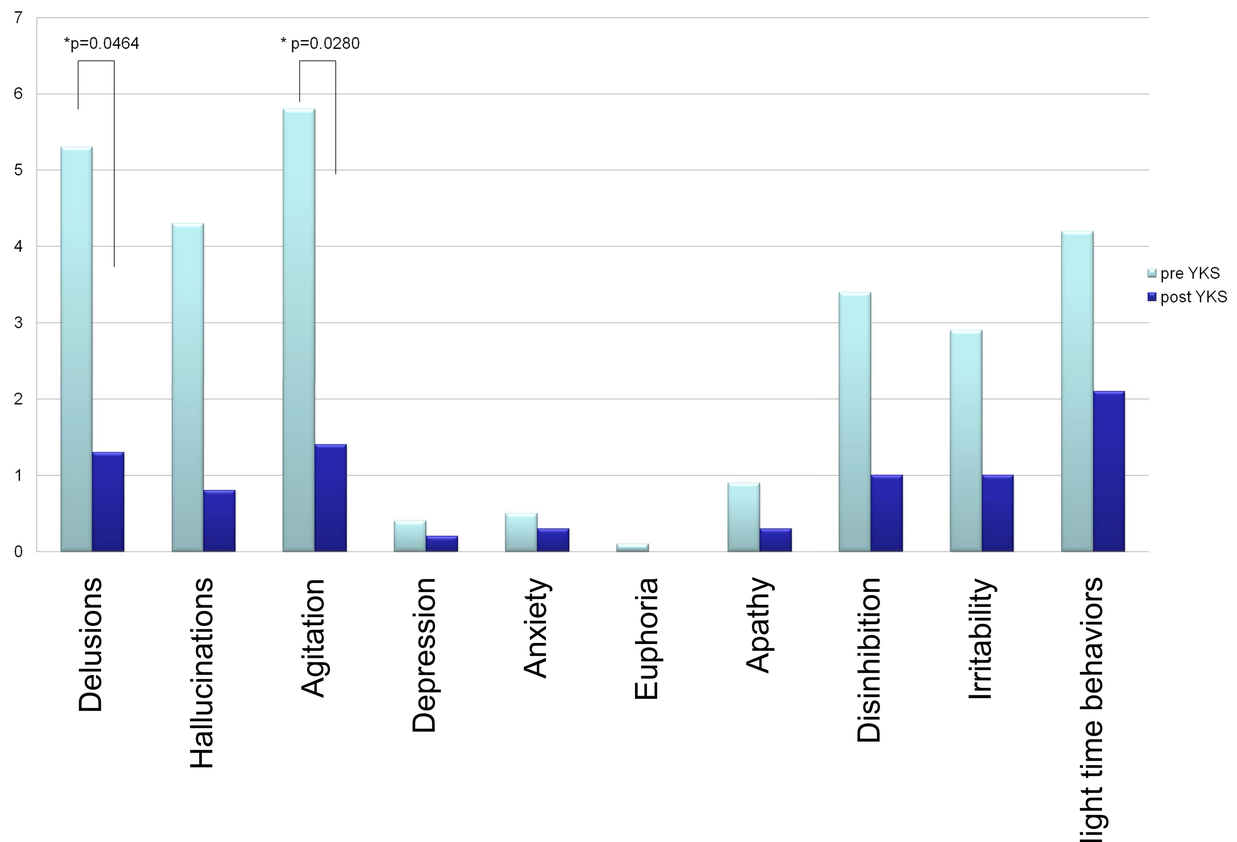


Figure2; Comparison of the symptoms of NPI before and after YKS treatment (N=11)



Conclusions

We showed that a traditional Chinese herbal medicine, YKS, significantly improved the symptoms of BPSD in CRF patients receiving hemodialysis without critical side effects. The pharmacokinetics of the ingredients contained in YKS need to be elucidated for more precise usage of YKS against BPSD in CRF patients.

References

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