Yokukansan Treatment of Chronic Renal Failure Patients Receiving Hemodialysis, with Behavioral and Psychological Symptoms of Dementia: An Open-Label Study

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Objective: The efficacy and safety of yokukansan (YKS) for chronic renal failure (CRF) patients receiving hemodialysis with behavioral and psychological symptoms of dementia (BPSD) was evaluated. Methods: Twelve CRF patients receiving hemodialysis with BPSD were recruited and 7.5 g of YKS powder was added to ongoing therapy with antipsychotics. Neuropsychiatric Inventory (NPI) criteria and Barthel Index before and after 4-week YKS treatment were compared. Results: Analysis of the mean score for NPI revealed a significant improvement during the period of YKS administration (25.3 ± 17.6 versus 8.36 ± 4.46; p = 0.0069). The mean score for the Barthel Index showed no significant difference during the period of YKS administration. Mean level of serum potassium was still within the normal range. No subjects had severe adverse reactions necessitating discontinuation from the study. Conclusion: Yokukansan significantly improved the symptoms of BPSD in CRF patients receiving hemodialysis without critical side effects. (Am J Geriatr Psychiatry 2013; 21:1082–1085)

Key Words: Yokukansan, dementia, chronic renal failure, hemodialysis, hyperkalemia

Individuals with end-stage chronic renal failure (CRF) have two- to sevenfold higher prevalence of cognitive impairment and dementia compared with the general population. 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. Behavioral and psychological symptoms of dementia (BPSD) are a significant burden to caregivers, and often relate to poor performance on activities of daily living, 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 effectiveness of the drug. The time required for neuroleptics to reach steady state is also lengthened when compared with 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 patients. Excessive potassium must be removed by hemodialysis so that 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.

Yokukansan (YKS) is an herbal medicine that was developed as a remedy for restlessness and agitation in children. Several clinical studies have revealed the efficacy of YKS for BPSD with Lewy body dementia, 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 at the Yoshida General Hospital, Kurayoshi Hospital, and the Miyoshi Clinic, Hiroshima, Japan. All subjects were required to have been diagnosed with CRF and to be receiving hemodialysis three 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, and 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 criteria before and after 4-week YKS treatment were compared. The activities of daily living of participants were evaluated using the Barthel 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**

**Efficacy**

A total of 12 patients were recruited for the present trial. A 79-year-old man who satisfied the diagnostic criteria of Alzheimer 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 the Neuropsychiatric Inventory scale revealed a significant improvement during the period of YKS administration (25.3 ± 17.6 versus 8.36 ± 4.46; *p* = 0.0069; Table 2). Delusions and feelings of agitation were significantly reduced (data not shown). The mean score for the Barthel index showed no significant difference during the period of YKS administration (47.6 ± 21.2 versus 50.4 ± 22.1; *p* = 0.1441; Table 2).

**Safety and Tolerability**

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. Subjects reported a few mild and transient adverse events, including nausea (1 case) and tiredness (1 case), and no subjects had severe adverse reactions necessitating discontinuation from the study.

**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. YKS was significantly effective for the symptoms of “delusion” and “agitation” in this study. Other groups have also revealed that YKS improved BPSD such as hallucination, agitation, anxiety, irritability, and abnormal behavior in patients with dementia including Alzheimer disease, in which the glutamatergic neurotransmitter system was perturbed. Takeda et al. showed that administration of YKS significantly suppressed the increase of extracellular glutamate and aspartate in the hippocampus of zinc-deficient rats. YKS improves age-related increased anxiety and enhances serotonergic and dopaminergic transmissions in the prefrontal cortex of aged rats, a model of BPSD. Previous information, as well as our clinical experience, suggests that YKS is a potential medication for prevention or cure of neurological diseases associated with excitotoxicity.

Glycyrrhetinic acid (GA) is one of the key extracts of YKS. Although GA is widely used for hepatic detoxification, taking excess GA leads to hypokalemia, also termed pseudoaldosteronism. Increased cortisol caused by GA administration in CRF patients engages colorectal mineral corticoid receptors and promotes potassium excretion from the colon and rectum instead of injuring the kidney. It is improbable that GA is easily dialyzed out of the circulation despite its low molecular weight (471 Da) as more than 99.9% of GA binds to albumin. Ninety-eight percent of ingested GA is observed in the discharged feces and less than 1% is discarded in the urine. GA, therefore, can be an ideal alternative potassium-removing agent for CRF patients receiving hemodialysis. The literature has shown that 6.5%–41.2% of CRF patients receiving hemodialysis were hyperkalemic; in the present study, however, blood potassium concentrations in all patients were within the normal range during the

**TABLE 1. Demographics and Clinical Characteristics of 11 Subjects Diagnosed With Dementia Receiving Hemodialysis Prior to Yokukansan Treatment**

<table>
<thead>
<tr>
<th>Age, mean ± SD, years</th>
<th>68.0 ± 7.3</th>
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<tbody>
<tr>
<td>Sex, N</td>
<td></td>
</tr>
<tr>
<td>Male</td>
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</tr>
<tr>
<td>Female</td>
<td>4</td>
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<td>Diagnosis, N</td>
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<tr>
<td>Alzheimer disease</td>
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<td>Vascular dementia</td>
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<tr>
<td>MMSE score</td>
<td>10.5 ± 6.0</td>
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<tr>
<td>Anti-psychotic use</td>
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<tr>
<td>Haloperidole, N</td>
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</tr>
<tr>
<td>Risperidone, N</td>
<td>3</td>
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<tr>
<td>Quetiapine, N</td>
<td>2</td>
</tr>
<tr>
<td>Perospirone, N</td>
<td>1</td>
</tr>
<tr>
<td>Number of antipsychotics, mean ± SD, N</td>
<td>1.18 ± 0.72</td>
</tr>
<tr>
<td>Dose of antipsychotic,a mean ± SD, mg/day</td>
<td>164.2 ± 152.4</td>
</tr>
</tbody>
</table>

**Notes:** MMSE: Mini-Mental State Examination.

**TABLE 2. Comparison of NPI, Bathel Index, Serum K⁺ Concentration Before and After Yokukansan Treatment (N = 11)**

<table>
<thead>
<tr>
<th></th>
<th>Before YKS Treatment</th>
<th>After YKS Treatment</th>
<th>p valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPI score</td>
<td>25.3 ± 17.6</td>
<td>8.36 ± 4.46</td>
<td>0.0069**</td>
</tr>
<tr>
<td>Bathel index score</td>
<td>47.6 ± 21.2</td>
<td>50.4 ± 22.1</td>
<td>0.1441</td>
</tr>
<tr>
<td>Serum K⁺ (meq/L)</td>
<td>3.89 ± 0.56</td>
<td>3.78 ± 0.46</td>
<td>0.6465</td>
</tr>
</tbody>
</table>

**Notes:** NPI: neuropsychiatric inventory; YKS: Yokukansan.
aWilcoxon signed-rank test was used.
YKS treatment period. These data demonstrate that administration of YKS to CRF patients on hemodialysis improved hyperkalemia, and that CRF patients, compared with subjects with normal renal function, are unlikely to suffer from enhanced side effects elicited by accumulated YKS.

The mechanism underlying alleviation of BPSD by YKS is considered a combined effect of its ingredients. Although it is unclear whether these ingredients bind to plasma proteins, and are therefore removed by hemodialysis, at least a portion of the dose must be retained in the circulation to remain effective. The pharmacokinetics of the ingredients contained in YKS need to be elucidated for more precise usage of YKS against BPSD in CRF patients.

References