Kampo medicine can improve quality of life and prolong hemodialysis implementation in patients with advanced-stage chronic kidney disease

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ABSTRACT

Cases: Chronic kidney disease (CKD) increases in an aging society and eventually leads to hemodialysis (HD). We present two cases of advanced CKD, successfully supported with Kampo medicine (KM), and resulting in delayed initiation of HD. To begin, a 58-year-old man with advanced CKD visited the Kampo clinic. His physical findings were general edema and oliguria. Kampo diagnosis showed spleen™ and kidney™ deficiencies with fluid™ retention and blood™ stasis (the superscript suffix [TM] indicates words (general and medical terms) that are used as Kampo medical terms). Second, a 70-year-old woman with advanced CKD had to transfer to the evacuation center because of the Great East Japan earthquake. Two weeks later, her body weight increased with edema and oliguria. Emergency HD was indicated; however, the area was broken down by the earthquake.

Outcome: As an alternative treatment, the first patient was administered KM to tonify the spleen™ and kidney™ functions with smoothing fluid™ and blood™. As a result, his serum creatinine (sCr) level decreased from 5.99 to 2.23 mg/dL after five months of administration. Finally, implementation of regular HD was initiated which was prolonged for three years. Similar to the first case, the second patient was prescribed KM; her sCr level decreased from 9.2 to 4.5 mg/dL after a month of administration. Finally, implementation of regular HD was initiated which was prolonged for two years.

Conclusion: Regular HD implementation was prolonged in advanced CKD patients using KM; thus, it is a supportive therapy for advanced CKD patients.

KEY WORDS: chronic kidney disease, hemodialysis, Kampo medicine, quality of life, support

INTRODUCTION

Chronic kidney disease (CKD) has increased along with growth of the proportion of elderly people in a super-aging society in Japan. Diabetes mellitus (DM), hypertension (HT), and other diseases can cause renal failure. In the case of advanced-stage CKD, it progresses slowly with no recovery despite Western medicine treatment, and eventually leads to hemodialysis (HD), peritoneal dialysis, or kidney transplantation [1]. Regular HD or peritoneal dialysis leads to a reduced quality of life (QOL). If alternative medicine can manage the symptoms related to CKD and delay the initiation of HD, it will contribute to improve the patient’s QOL and the healthcare economy. As an integrative therapy, in several clinical practice guidelines Kampo medicine is recommended for many diseases, conditions, and symptoms[2–5].

The World Health Organization published the eleventh revision of the International Statistical Classification of Diseases and Related Health Problems in 2019, and traditional medicine™ was featured for the first time as a module [6] (the superscript suffix [TM] indicates words (general and medical terms) that are used as Kampo medical terms). Traditional medicine, including Japanese Kampo medicine, has been used in combination with Western medicine for many intractable diseases and conditions as an integrative medicine, and it will be widely applied as a new approach from now on. Herein, we present two cases of advanced-stage...
CKD successfully managed with Kampo medicine, resulting in a delayed initiation of HD.

**CASE PRESENTATION**

The first case presents a 58-year-old man who has been on treatment for 10 years because of DM, HT, and CKD. His renal function has been slowly worsening, and blood sampling revealed an advanced-stage CKD with a serum blood urea nitrogen (BUN) level of 98.6 mg/dL and a serum creatinine (sCr) level of 6.35 mg/dL. Treatment results with Western medicine appeared to be limited, and physicians introduced Kampo medicine. He had received treatment with calcium channel blockers, β-blockers, sulfonylurea, furosemide, and sodium polystyrene sulfonate from a Western medicine doctor before being introduced to our clinic. At his first visit to our clinic, he took only a calcium channel blocker and a β-blocker. The physical findings were general edema and oliguria, with a body mass index of 37.1. Home blood pressure showed systolic pressure ranging from 150 to 160 mm Hg and diastolic pressure from 80 to 90 mm Hg. A urinary test showed a positive urine protein level of 2+. Serum albumin levels were not measured. Computed tomography and ultrasound doppler imaging performed by a prior doctor showed bilateral kidney atrophy without significant renal artery stenosis. Subjective symptoms included thirst, appetite loss, general fatigue, and a cold feeling in the lower legs. Physical examination revealed massive edema, dry mouth, and oliguria. Tongue diagnosis showed teeth marks on the tongue and dilatation of the sublingual vein. Pulse diagnosis showed a weak pulse with sinking, thin, and slipping findings. These findings suggested a spleen™ and kidney™ deficiency with fluid™ retention and blood™ stasis in the Kampo diagnosis [7]. As an alternative treatment, the decoction-type Kampo medicine, hachimijiogan (HJG), and hikaibunseiin (HBI) were administered to tonify the spleen™ and kidney™ function with smoothing fluid™ and blood™. Originally, HJG was used for kidney deficiency and HBI, for kidney yang deficiency with dampness. The amount of crude drugs per day included in the formula is as follows: Astragalus Root 20 g, Ginseng 6 g, Cinnamon Bark 6 g, Processed Aconite Root 6 g, Cornus Fruit 10 g, Dioscorea Rhizome 15 g, Alisma Tuber 10 g, Poria Sclerotium 10 g, Moutan Bark 10 g, Rehmannia Root 10 g, Ophiopogon Root 10 g, Citrus Unshiu Peel 10 g, Atractylodes Rhizome 10 g, Peach Kernel 5 g, Safflower 5 g, Japanese Angelica Root 10 g, Plantago Seed 10 g, Dioscorea hypoglauca Rhizome 10 g, Earthworm 5 g. Some additions and subtractions were made depending on his conditions. As a result, his symptoms were relieved and serum creatinine level decreased from 5.99 to 2.23 mg/dL five months after the administration (Fig. 1). Regular HD was prolonged for three years.

In the second case, a woman aged 70 years has been on treatment for five years due to CKD caused by DM. HD was initiated because of the advanced-stage CKD which was treated with a calcium channel blocker, angiotensin II receptor blocker (ARB), furosemide, and sodium polystyrene sulfonate. However, because of the Great East Japan earthquake of March 11, 2011, she had to transfer to the evacuation center and stay there. Two weeks after the earthquake, her body weight increased with edema and oliguria. Blood sampling showed a blood urea nitrogen (BUN) level of 61.6 mg/dL, a sCr level of 9.2 mg/dL, and a serum potassium level of 7.5 mEq/L. Re-testing of blood samples also showed high a serum potassium level. With careful biomonitoring, she received hydration with high-dose furosemide under sodium polystyrene sulfonate administration but ARB administration was stopped. After this treatment, the levels of sCr and serum potassium remained high. The physician decided that the patient undergo an emergency HD because of the lack of...
urine, edema, and dyspnea. Unfortunately, as a result of the large earthquake and tsunami, there were no medical facilities that could support the administration of HD. Treatment using Western medicine was limited, and the physician diagnosed and treated her with Kampo medicine. Subjective symptoms included thirst, appetite loss, general fatigue, and a cold feeling in the lower legs. Physical examination revealed marked edema, diarrhea, and oliguria. Tongue diagnosis showed reddish teeth marks on the tongue, whitely coated. Pulse diagnosis showed a weak pulse with sinking, thin, and slipping findings. These findings suggested kidney deficiency with cold fluid retention in the Kampo diagnosis. The diagnosis was similar to that in the first case. The physician prescribed the same Kampo medicine, HJG, and HBI, as an alternative treatment to support kidney function and smooth fluid retention. The amount of crude drugs per day included in the formula is as follows: Astragalus Root 10 g, Glycyrrhiza 10 g, Cinnamon Bark 6 g, Rehmannia Root 10 g, Cornus Fruit 6 g, Dioscorea Rhizome 10 g, Rhubarb 5 g, Alisma Tuber 6 g, Smilax Rhizome 10 g, Polyposorus Sclerotium 6 g, Citrus Unshiu Peel 6 g, Ginseng 6 g, Pinellia Tuber 6 g, Poria Sclerotium 10 g, Processed Aconite Root 6 g, Moutan Bark 6 g, Salvia miltiorrhiza Root 10 g, Dioscorea hypoglauca Rhizome 10 g. Some additions and subtractions were made depending on her conditions. After the prescription, her urinary output gradually increased, and sCr level decreased from 9.2 to 4.5 mg/dL (Fig. 2) a month after the administration. Regular HD administration was prolonged for two years.

In both these cases, we present only representative prescriptions because they are too complicated to describe in detail, although some addition and subtraction of crude drugs was performed at each consultation.

**DISCUSSION**

We present two cases that were successfully supported with Kampo medicine to improve the QOL, which resulted in a delayed initiation of new HD. The latest number of new patients introduced to HD was 38,556 [8], and the number of patients receiving HD was 344,640 [9] in 2019 in Japan. Regular HD can improve the condition of patients with advanced-stage CKD; however, it restricts their QOL. If alternative medicine can support symptoms related to CKD and delay the initiation of HD, it will contribute to improve the patient’s QOL. Furthermore, approximately 57,000 dollars per patient per year in medical costs is needed to maintain regular HD; however, the annual cost of Kampo medicine is one-thirtieth that of regular HD in Japan. Thus, if alternative treatment can delay the initiation of dialysis, it will also contribute to health care economy. Several reports have suggested that Kampo medicine is advantageous in terms of medical cost, estimated using a national database [10–12]. Taking these points into account, supportive Kampo medicine treatment can contribute to patients’ QOL and to social economy, as shown in our present cases.

In the present cases, both patterns of Kampo medicine are spleen and kidney deficiencies according to the subjective and objective findings. Spleen deficiency is defined as one of the organs with the function of creating qi from water and grain and functions to smooth blood flow and prevent leakage from blood vessels in Kampo medicine [7]. However, kidney deficiency is defined as one of the organs, whose functions are to regulate fluid metabolism and maintain breathing, and regulate excretion in Kampo medicine [7]. In cases of severe spleen deficiency and kidney deficiency, the fluid in the body cannot be controlled, and this manifests as CKD. Supporting spleen and kidney functions with Kampo medicine can facilitate diuresis and suppress urinary toxicity in Kampo theory.

The modified Kampo medicine HJG with Plantago seed, Phellodendron bark, Atractylodes rhizome, Nelumbo seed, Salvia miltiorrhiza root, Dioscorea septemloba, and Acori Rhizoma was used for patients with advanced-stage CKD in the present case report. The prescription is named HJG and HBI, and it could supplement the spleen and kidney and improve water balance and the urinary condition, at least for a while. The formula of HJG and HBI was originally named hachimijigangoteishihikaibunseiin, in which the concept of traditional medicine is clearing heat and relieving dampness. Combined with HBI, the effects of clearing heat and relieving dampness are induced in the lower energizer, which includes the kidney, bladder, and gallbladder [7]; and the effect of HJG was enhanced with HBI. In other words, some of these concepts are considered anti-inflammatory, protecting tissues and organs, and supporting metabolism and diuretics in Western medicine. The target conditions for using this formula are frequent urination, burning pain during urination, dysuria, cloudy urine, and yellowish tongue moss.

Oka et al. reported several mechanisms for CKD in HJG, which is part of the Kampo medicine used for the present cases [13]; HJG suppresses urinary protein excretion, increases the protein volume of hypoxia-inducible factor (HIF)-1α in the renal cortex, increases the expression of
HIF-1α at high dose, increases vascular endothelial growth factor and glucose transporter 1, and targets genes of HIF-1α. Yamabe et al. reported that HJG protects against the progression of chronic renal failure by reducing uremic toxins and elevating antioxidative enzyme activity, such as superoxide dismutase and catalase, and prevents glomerular sclerosis and progressive renal fibrosis [14].

*Plantago* seed has anti-inflammatory, cellular antioxidant, and radical-scavenging properties [15]. *Phellodendron* bark has anti-inflammatory and antigout effects [16]. *Atractylodes* rhizome has anti-hypertensive, anti-platelet, anti-inflammatory, anti-microbial, and anti-pyretic activities [17]. *Nelumbo nucifera* is effective against microbial infections, diabetes, inflammation, atherosclerosis, and obesity [18]. *Salvia miltiorrhiza* root has properties of anti-oxidation, anti-inflammatory, phytoestrogenic activity, and vasodilation, and regulates metabolic function [19]. *Dioscorea septemloba* has an anti-inflammatory effect and facilitates the excretion of uremic acid and lower uremic acid levels by upregulating the expression of organic anion transporting protein 1 [20,21] *Acori Rhizoma* promotes nitric oxide production and has an antioxidative effect [22]. *Radix Astragali* has diuretic, anti-inflammatory, antihypertensive, and vasodilatory effects. Zhang et al. suggested that *Astragalus* with conventional medicine may have positive effects in reducing proteinuria, increasing hemoglobin levels, decreasing blood pressure, and improving serum albumin levels [23]. These effects protect the kidneys and, along with *Dioscorea hypoglauca* rhizome, contribute to the prevention of chronic renal failure. These additional crude drugs enhance the clinical effect of HJG by lowering serum uremic acid and urea levels, anti-inflammatory and anti-oxidant effects, and vasodilation.

Nagasaka et al. also reported that Kampo medicine improved sCr levels after six months of administration in patients with CKD [24]. The mean sCr level of 3.9 mg/dL significantly decreased to 3.5 mg/dL in 28 patients with CKD with the Kampo medicine yozinkodakuto. They also mentioned the possibility of using Kampo medicine to prolong the implementation of HD. Yozinkodakuto includes similar crude drugs and was developed from the Kampo medicine used in the present case report. These reports support the clinical efficacy and some of the mechanisms of its effect on Kampo medicine for advanced-stage CKD; however, the detailed mechanism remains unknown. The present report comprises remarkable effective cases in advanced-stage CKD supported with Kampo medicine and is the first report showing the efficacy of HJG and HBI for advanced-stage CKD. Because factors other than Kampo medicine treatment cannot be ruled out, further studies are needed.

**CONCLUSION**

We present two cases of advanced-stage CKD successfully managed with the Kampo medicines HJG, and HBI to improve the QOL, resulting in delayed introduction to regular HD. Kampo medicine according to the Kampo diagnosis appeared to support advanced-stage CKD and is considered one of the choices of supportive treatment.

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**CONFLICT OF INTEREST**

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**ETHICS APPROVAL**

The cases of this report were approved by Ethics Committee of Tohoku University Hospital (Certificate No. 20296).

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