KAMPO MEDICINE

Analysis of Treatment with *Astragalus Membranaceus* Powder in Patients with Chronic Kidney Disease

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ABSTRACT

Objective: **This study was conducted to investigate the clinical indication of *Astragalus membranaceus* (AM) administration for chronic kidney disease (CKD) patients in relation to the primary cause of the disease.**

Design: **This was a retrospective cohort study.**

Materials and Methods: **CKD patients who visited our Kampo clinic after 2013, whose serum creatinine (SCr) level of ≥ 1.0 mg/dl persisted for ≥ 3 months, and who could take AM powder (3.0-6.0 g/day) for ≥ 6 months were analyzed. A decrease in SCr of ≥ 10% 6 months after AM administration, was judged "effective." The primary causes of CKD were inferred from medical history, blood, and urine findings.**

Results: **Twenty-two CKD patients were analyzed, and 10 of the cases were associated with hypertension. AM administration was effective in 12 of 22 cases, of which 8 were associated with hypertension, 1 with multiple organ failure after urinary tract infection, and 3 had unclear causes.**

Conclusions: **Oral administration of AM powder may reduce SCr level of patients with CKD caused by hypertension.**

KEY WORDS

Kampo medicine, chronic kidney disease (CKD), *Astragalus membranaceus*, hypertension, serum creatinine

INTRODUCTION

In recent years, end-stage renal failure requiring dialysis and renal transplant has been increasing all over the world, and this not only poses a major threat to human life, but also causes a significant increase in medical costs for its treatment. Chronic kidney disease (CKD) is the main cause of end-stage renal failure, and the primary causes of CKD are mainly diabetes, chronic nephritis, and hypertension. Early diagnosis and therapeutic intervention are important in CKD, because its renal function often declines without symptoms. However, in modern Western medicine, the treatments for CKD mainly involve the control of primary causes, general therapy such as lifestyle improvement and exercise, and dietary therapy such as salt reduction and energy-restricted diet. Nevertheless, effective remedies to control the progression of CKD are not yet generally accepted.

Therefore, we focused on the medicinal plant *Astragalus membranaceus* (AM), which is widely used for CKD in Chinese medicine. We have previously reported a basic study that showed AM suppressed acute kidney injury induced by cisplatin in old mice[1)], and a clinical case in which AM improved serum creatinine (SCr) level and estimated glomerular filtration rate (eGFR) in a CKD patient[2)]. Although there are some reports, including ours, that oral administration of AM clinically improves renal function in CKD patients, few studies have examined the indication of oral AM administration for the primary causes of CKD. In this study, we aimed to retrospectively analyze CKD patients who were orally administered AM powder and to examine the clinical indication in relation to the causes.

METHODS

This was a retrospective cohort study. We studied CKD patients who visited our Kampo clinic after 2013 with various complaints, whose SCr level of 1.0 mg/dl or more persisted for 3 months or more, who could take AM powder continuously for 6 months or more, and who did not change their medication, including Western medicine, from 3 months before to 6 months after AM administration. The primary causes of CKD were inferred from medical history, blood, and urine findings. AM powder was added to the Kampo medicines given to each patient, adjusted from 3.0 g up to 6.0 g/day, and orally administered twice or three times a day. AM powder was provided by Uchida Wakanyaku Ltd. The treatment was determined "effective" if SCr level was stably reduced by 10% or more 6 months after AM administration. No statistical analysis was performed in this study. This study was approved by the Institutional Review Board for Clinical Research of Tokai University and conformed to the principles of the Helsinki Declaration.

RESULTS

Twenty-two CKD patients (16 male and 6 female, mean age 69 ± 14 years, range 29-87 years) were analyzed. The stages of CKD were from G3a to G5. The primary causes were hypertension in 10 cases, including 2 cases with diabetes, 1 case with drug-induced nephropathy, and 1 case after renal cancer surgery, and only diabetes, IgA nephropathy, systemic lupus erythematosus (SLE), pelvic kidney, multiple organ failure (MOF) in 1 case each, and unclear causes in 7 cases. The SCr at the start of AM administration was 1.11 to 2.51 (mean; 1.51 ± 0.38) mg/dl and the eGFR was 14.8 to 56.8 (mean; 36.8 ± 11.2) ml/min/1.73 m^2.

Treatment with AM was effective in 12 of 22 cases, of which 8 were CKD associated with hypertension, 1 with MOF after urinary tract

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Table 1: Outcomes of 22 CKD patients treated with *Astragalus membranaceus* powder

No.	Age	Sex	Underlying condition	Dose of AM (g/day)	Duration of administration	Primary cause	Serum creatinine (mg/dl)			eGFR (ml/min/ 1.73 m²)	CKD Stage	Urinary findings			Judgement	Notes
							Pre	Post	improvement rate (%)			Protein	Sugar	Uric blood		
1	87	F	Hyperlipidemia	3.0	2018.11-	**Hypertension**	1.26	0.95	24.6	30.9	G3b	-	-	-	Effective	
2	80	F	Hyperlipidemia	3.0	2020.05-	**Hypertension**	1.39	1.13	18.7	28.4	G4	-	-	-	Effective	
3	62	M	Cerebrovascular disease	3.0	2016.09-	**Hypertension**	1.40	1.05	25.0	41.4	G3b	-	-	-	Effective	
4	81	F	Sciatica	4.0	2018.07-	**Hypertension**	2.51	1.32	47.4	14.8	G5	-	-	-	Effective	
5	58	M	None	4.0	2019.12-	**Hypertension**	1.21	1.03	14.9	49.1	G3a	-	-		Effective	
6	71	M	Benign prostatic hyperplasia	3.0	2018.03-	**Hypertension**	1.42	1.17	17.6	38.9	G3b	-	-	±	Effective	
7	73	F	CML	3.0	2017.10-2020.04	**Hypertension** / Drug induced	1.64	1.47	10.4	24.2	G4	-	-	-	Effective	
8	81	M	Renal cancer	3.0	2018.08-	**Hypertension** / Renal cancer	1.80	1.48	17.8	28.9	G4	-	-	-	Effective	
9	82	F	Dementia	3.0	2017.08-	UTI → MOF	2.23	1.56	30.0	16.8	G4	2+	-	-	Effective	
10	77	M	Prostate cancer	4.5	2014.04-	Unclear	1.28	1.04	18.8	42.6	G3b	-	-	-	Effective	
11	70	M	Psychogenic dysautonomia	3.0	2016.02-	Unclear	1.28	1.00	21.9	43.7	G3b	-	-	-	Effective	
12	69	M	AMI	3.0	2016.04-2020.01	Unclear	1.71	1.48	13.5	32.0	G3b	-	-	-	Effective	
13	77	M	Thyroid cancer	4.0	2019.02-	**Hypertension** / DM	1.68	1.38	17.9	31.6	G3b	-	-	-	Ineffective	Unstable data
14	81	M	Spinal canal stenosis	3.0	2020.06-	**Hypertension** / DM	1.37	1.43	-4.4	38.9	G3b	+	-	-	Ineffective	
15	73	M	DM	4.0	2020.05-	DM	1.25	1.25	0.0	44.4	G3b	+	±	-	Ineffective	
16	65	M	Bronchial asthma	3.0	2015.11-	IgA nephropathy	1.29	1.20	7.0	44.3	G3b	+	-	+	Ineffective	
17	35	F	SLE	3.0	2017.12-	SLE	1.27	1.21	4.7	39.8	G3b	+	-	-	Ineffective	
18	29	M	Hyperlipidemia	3.0	2013.06-	Pelvic kidney	1.27	1.17	7.9	56.8	G3a	+	-	-	Ineffective	
19	70	M	Bladder cancer	2.0	2019.02-	Unclear	1.21	1.11	8.3	46.5	G3a	-	-	-	Ineffective	
20	78	M	Prostate cancer	6.0	2017.09-	Unclear	2.22	1.26	43.2	23.2	G4	±	-	-	Ineffective	Unstable data
21	59	M	Chronic pancreatitis	3.0	2016.11-2018.03	Unclear	1.11	1.11	0.0	53.7	G3a	+	-	-	Ineffective	
22	66	M	Rheumatoid arthritis	3.0	2014.11-	Unclear	1.44	1.26	12.5	39.1	G3b	-	-	-	Ineffective	Unstable data

infection, and 3 had unclear causes. By dividing the primary causes of CKD into hypertension and non-hypertension, AM was effective in 8 of 10 hypertension-associated CKD cases and in 4 of 12 non-hypertension-associated CKD cases. No adverse reactions due to AM were observed during follow-up (Table 1).

DISCUSSION

CKD is a major public health issue worldwide. Current standard therapies to delay CKD progression include dietary protein restriction and administration of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers to help control blood pressure and confer additional renoprotective effects. Despite such interventions, CKD incidence and mortality rates continue to increase globally. AM is a kind of podded plant used in traditional medicine in East Asian countries including China, South Korea, and Japan, and it may reduce SCr level and increase eGFR in CKD patients. In China, AM is one of the traditional medicinal plants widely used as a remedy for kidney diseases, and 3 meta-analyses on AM therapy for CKD have been reported. Two of these meta-analyses targeted diabetic kidney disease[3,4] and the other did not mention CKD primary causes[5]. These studies concluded that the routes of administration of AM were mostly injection, and that the treatment reduced the patients' SCr and urinary protein levels. Furthermore, the report stated that the effect and safety of oral AM preparations were uncertain and the reducing effect on SCr levels was unclear, because the number of studies for oral administration of AM was so limited[4].

In Japan, only a few small clinical studies of AM therapy for CKD patients were reported, showing that all routes of AM administration were oral, using decoction or powder for safety and ethical reasons[2,6-9], and that even oral administration of AM reduced SCr levels in CKD patients. As for its long-term effects, there were reports that AM might delay dialysis induction[6] and could maintain stable levels of eGFR and delay the initiation of renal replacement therapy in patients with progressive CKD stage[4,7].

Diabetic nephropathy is the most frequent cause of CKD, with the typical histopathological findings being thickening of glomerular basement membrane, enlargement of mesangium, thickening of tubular basement membrane, enlargement of interstitium, and exudative lesions of small blood vessels. On the other hand, in hypertensive CKD, typical findings are sclerotic changes in renal arterioles, fibrosis of the renal interstitium due to a decrease in renal blood flow, glomerular sclerosis, and further progress into renal parenchyma sclerosis, that is, hypertensive nephrosclerosis. Even though the clinical features of both types of CKD are similar, the renal pathological findings are essentially different depending on the primary causes, and thus it is expected that there will be a difference between the two in the effect of improving renal function by AM administration.

Regarding the improvement effect of AM on renal dysfunction in relation to the primary cause, two meta-analyses have been conducted only for patients with CKD caused by diabetes[3,4], and one clinical report of SCr-improving effects for chronic kidney allograft dysfunction[8]. However, no study has compared the effects of AM with each primary cause of CKD, and there is no report suggesting that AM is effective regardless of proteinuria or diabetes in CKD patients[9].

In this retrospective study, we examined the primary causes of CKD in terms of hypertension and non-hypertension, based on laboratory findings and medical history, resulting that 6 months of AM oral administration was effective in 8 of 10 hypertension-associated CKD patients and only 4 of 12 non-hypertension associated cases. This result strongly suggests that oral administration of AM was effective in improving renal function in CKD patients caused by hypertension, even if statistical analysis was not performed because of the selection bias. However, in only 3 patients the cause was diabetes, which is the most common primary cause of CKD, and AM therapy for those patients was ineffective. The reason why there were few patients with diabetic nephropathy may be that these patients are usually treated at an outpatient clinic for diabetes in large general hospitals such as our university hospital, and rarely visit a Kampo outpatient clinic.

Chinese data mining-based analysis shows that the most frequently prescribed core herbs for CKD treatment were *Dioscoreae Rhizoma*, *Herba Hedyotis Diffusae*, *Herba Serissae*, *Poria*, *Rhizoma Atractylodis Macrocephalae*, *Radix Pseudostellariae*, and *Forsythiae Fructus*, in addition to AM[10]. In Japan, there is a report of chronic renal failure successfully treated with rhubarb[11] based on the effects of rhatannin on urea metabolism[12] and the effects of (-)-epicatechin 3-O-gallate and procyanidin B-2 3,3'-di-O-gallate to improve renal failure[13]. However, a meta-analysis on rhubarb therapy for CKD in China concluded there was no current evidence to support any recommendation for its use[14], and due to its remarkable cathartic effect rhubarb is actually difficult to apply even if it is used clinically[15].

The major limitation of this study was that the selection bias may be significant, because the design was as a retrospective cohort study. Other limitations included the small number of CKD patients who visited our Kampo outpatient clinic and a large bias in the distribution of primary causes of CKD, which prevented statistical analysis in this study. In addition, since many patients had been treated for underlying diseases in other hospitals or clinics, there were many cases in which the primary causes of CKD could not be fully identified. Furthermore, the effects of AM administration were not examined by renal histopathology in this study. These limitations should be resolved in the future.

In the next step, to clarify the clinical indication of AM as a therapeutic agent for CKD, it is necessary to conduct a prospective study in more patients with CKD and to examine histopathological changes in the kidney.

CONCLUSIONS

AM was previously reported to improve renal function in CKD patients, but little was mentioned about the primary causes of CKD. This study suggested for the first time that oral administration of AM powder may improve renal function specifically in CKD caused by hypertension.

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