

Original Article

Efficacy of short-term cordyceps sinensis for prevention of contrast-induced nephropathy in patients with acute coronary syndrome undergoing elective percutaneous coronary intervention

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Abstract: Contrast-induced nephropathy (CIN) is one of the major causes of hospital-acquired acute renal failure. The pathophysiological mechanism of CIN remains unknown. There has been little evidence regarding the effects of Traditional Chinese Medicine (TCM) on CIN. Cordyceps sinensis (CS), a traditional Chinese herb, has been widely used clinically for the prevention of the progression of renal failure. We performed a prospective, randomized controlled trial to investigate the role of CS in the prevention of CIN in patients with acute coronary syndrome (ACS) undergoing elective percutaneous coronary intervention (PCI). The 150 ACS patients were randomly assigned to three groups, basic treatment group (n=51), standard CS therapy group (n=49, corbrin capsule 2 g, 3 times/d were used 3 days before and after angiography), and intensive CS therapy group (n=50, corbrin capsule 3 g, 3 times/d were used 3 days before and after angiography). Renal function was assessed at the time of hospital admission and on days 1, 2, and 3 after PCI. CIN occurred in 13 of 150 patients (8.67%). The incidence of CIN was lower in the CS treatment groups than in the basic treatment group ($P<0.05$), and a significant decrease in the incidence of CIN in the intensive CS therapy group was shown ($P<0.01$). In conclusion, prophylactic treatment with CS during the peri-procedural stage in ACS patients undergoing elective PCI has a preventive role against CIN, and intensive CS therapy could be more effective.

Keywords: Cordyceps sinensis, contrast induced nephropathy, acute coronary syndrome, percutaneous coronary intervention

Introduction

The dramatic evolution and improvement in coronary angiography and percutaneous coronary intervention (PCI) have resulted in the increasingly frequent use of these modalities in recent years [1]. However, contrast-induced nephropathy (CIN) remains one of the most important clinical complications associated with the intravascular administration of radio contrast media [2]. CIN is an adverse event that results in increased health care costs, prolongs hospital length of stay, and increases both short- and long-term morbidity and mortality, even after adjustment for other co-morbidities. CIN has become the third leading cause of hospital acquired acute renal failure. The reported incidence of CIN ranges from 2% in low-risk

populations to 50% in high-risk population [3]. The risk factors for CIN are pre-existing renal failure, presence of diabetes mellitus, excess volume of contrast medium used, dehydration, anemia, congestive heart failure, gender, advanced age, and simultaneous usage of nephrotoxic drugs [4]. Once CIN develops, hydration status optimization is the only proven strategy to prevent it, and no other adjunctive mechanical or medical treatment specifically targets CIN. The main goal for clinicians is to find preventive measures [5].

Traditional Chinese medicine (TCM) has evolved into a well-developed, coherent system of medicine that uses several modalities to treat and prevent illness. Herbal medicine has been an integral part of TCM for more than 2500 years.

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Many herbal formulations have been developed and are used in the treatment of pre-end stage renal failure [6]. *Cordyceps sinensis* (CS), a time-honored tonic food and herbal medicine in China, can improve the microcirculation, increase the tolerance to ischemia in patients with microcirculatory disorders [7]. It is widely used in the therapy for treating acute glomerulonephritis and diabetic nephropathy, and has shown protection of renal function [8]. There have been few clinical trials to evaluate the role of TCM in preventing patients with acute coronary syndrome (ACS) from CIN. Therefore, we performed a prospective, randomized controlled trial to investigate the role of CS in the prevention of CIN in patients with ACS undergoing elective PCI.

Materials and methods

Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee of Tianjin Nankai Hospital (Tianjin, China), and conformed to the principles outlined in the Declaration of Helsinki. All participants were informed the details of the study and signed the written informed consents.

Study population

The present study was conducted at the Department of Cardiology at Tianjin Nankai Hospital from August 2012 to July 2014. According to a random number table, 150 eligible patients with ACS were divided randomly into 3 groups, basic treatment group (n=51), standard CS therapy group (n=49, corbrin capsule 2 g, 3 times/d were used 3 days before and after PCI), and intensive CS therapy group (n=50, corbrin capsule 3 g, 3 times/d were used 3 days before and after PCI). Subjects had to be ≥ 18 years and ≤ 75 years of age. ACS was diagnosed according to the criteria issued by American Heart Association, which includes acute myocardial infarction and unstable angina pectoris. This study only involved those patients with unstable angina pectoris and myocardial infarction attacked more than 7 days, excluding the cardiac shock or state supported by device, such as intra-aortic balloon pump (IABP). The exclusion criteria included patients who were hyperpyrexia or allergic to iodine or who had one of the following: severe kidney failure, severe congestive heart failure,

severe liver failure, disorders of the immune system, tumors, and blood diseases.

Intervention

All patients were hydrated with intravenous half-isotonic saline at a rate of 1 mg/kg per hour for 12 hours before and 12 hours after coronary catheterization. Patients in the CS group received corbrin capsule (Hangzhou east China pharmaceutical co., Ltd.). The decision to use aspirin, clopidogrel, beta-blockers, low-molecular-weight heparin preparations, angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists, and statins was left to the discretion of interventional and ward cardiologists, as directed by international guidelines. Interventional procedure was performed according to standard clinical practice using the femoral or radial approach. All procedures were performed with the use of iso-osmolar nonionic contrast media iodixanol (Visipaque, 320 mg iodine/mL, GE Healthcare, Shanghai, Co., Ltd.). Volume of contrast media was recorded for all patients during catheterization.

Outcome assessment

Serum levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), hemoglobin, glycosylated hemoglobin, blood glucose, and uric acid were assessed at the time of hospital admission. Serum creatinine (Scr) and estimated glomerular filtration rate (eGFR) were assessed at the time of hospital admission and 1, 2, and 3 days after PCI. Values of kidney injury molecule-1 (KIM-1), interleukin (IL) 18 and neutrophil gelatinase-associated lipocalin (NGAL) in urine were recorded before and one day after PCI in patients of three groups. The eGFR was calculated by using the Modification of Diet in Renal Disease (MDRD) equation: $eGFR (ml^{-1} \cdot min^{-1} \cdot 1.73 m^{-2}) = 186 \times serum Cr (mg/dl)^{-1.154} \times age (years)^{-0.203} (\times 0.742 \text{ for female subjects})$ [9].

Study end points

The primary end point of the study was the incidence of CIN, which was defined as a relative increase of $\geq 25\%$ or an absolute increase of Scr $\geq 44.2 \mu mol/L$ compared to baseline Scr levels after PCI within 3 days.

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Table 1. Baseline clinical and procedural characteristics of study patients

Characteristics	Basic treatment Group (n=51)	Standard CS therapy Group (n=49)	Intensive CS therapy Group (n=50)	F/ χ^2	P
Gender (Men/Women)	27/24	28/21	26/24	0.723	0.53
Age (yrs)	64.59±5.72	63.95±4.27	65.13±6.26	0.685	0.48
BMI (kg/m ²)	27.19±5.72	26.91±6.24	28.03±8.07	0.383	0.32
Hemoglobin (g/L)	129.18±10.18	130.18±9.76	132.18±11.39	0.463	0.39
Hypertension (%)	33 (64.71)	32 (65.31)	34 (68.00)	0.117	0.18
Cholesterol (mmol/L)	4.83±1.24	4.76±1.72	4.47±1.28	0.825	0.62
Triglycerides (mmol/L)	1.86±0.95	1.77±0.86	1.48±0.87	0.318	0.27
LDL-C (mmol/L)	2.75±0.94	2.83±0.41	2.57±1.06	0.382	0.31
HDL-C (mmol/L)	1.16±0.34	1.17±0.28	1.18±0.37	0.558	0.48
Blood glucose (mmol/L)	5.68±1.66	5.32±1.75	5.27±2.32	0.667	0.52
Glycosylated hemoglobin (%)	5.86±0.93	6.19±0.86	5.97±0.85	0.582	0.49
VOCM (ml)	246.87±49.76	248.86±48.68	250.85±50.73	0.573	0.48
LVEF (%)	59.27±11.63	58.74±11.86	61.32±12.08	0.629	0.55
Hydration volume (ml)	845±156	873±136	857±143	0.595	0.50

Notes: BMI, Body Mass Index; VOCI, volume of contrast medium; LVEF, left ventricular ejection fraction.

The secondary end point was 25% or greater reduction in the eGFR compared to baseline, which was calculated by using MDRD equation and Scr obtained before PCI and within 3 days after PCI.

Statistical analyses

Continuous variables and categorical variables are expressed as the mean \pm standard deviation (SD) and percentages, respectively. All samples are tested to ascertain if they followed a normal distribution. Categorical variables are compared using the χ^2 test or the Fisher exact test when appropriate. One-way analysis of variance (ANOVA) was applied for the analysis of continuous variables among the three groups. *P* values <0.05 (2-tailed) are considered statistically significant. All statistical analyses were performed using SPSS software version 13.0 (SPSS, Chicago, IL, USA).

Results

Safety evaluation

In the current study, no patients developed clinical renal failure or needed hemodialysis. No arrhythmia, blurred vision, palpitation, thirst, or retention of urine was found in the CS treatment groups. Patients in the CS treatment groups had no adverse reaction during the procedure.

Baseline clinical characteristics

Between August 2012 and July 2014, a total of 150 eligible patients were screened. They were randomized to the basic treatment group (n=51), standard CS therapy group (n=49), and intensive CS therapy group (n=50). Baseline demographics and clinical characteristics were similar among the three groups, with no significant differences observed (*P*>0.05, **Table 1**).

Changes in Scr and eGFR

All Scr levels were increased significantly after PCI, the peak value occurred at day 2, and then began to decrease (**Table 2**). The intensive CS therapy group tended to have a lower Scr than the standard CS therapy group and basic treatment group at day 2 after PCI (*P*<0.05). There was no significant difference between the basic treatment group and the standard therapy group (*P*>0.05). Scr levels were higher than baseline level at day 3 but without a significant difference among the groups (*P*>0.05).

All eGFR levels were decreased significantly after PCI (**Table 2**). The eGFR levels were significantly higher in the intensive CS therapy group than in the standard CS therapy group and basic treatment group at day 2 after PCI (*P*<0.05). There was no significant difference between the basic treatment group and the standard therapy group (*P*>0.05). All eGFR levels were lower than baseline levels at day 3, but

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Table 2. Changes in Scr and eGFR

Characteristics	Basic treatment Group (n=51)	Standard CS therapy Group (n=49)	Intensive CS therapy Group (n=50)
Baseline Scr (μmol/L)	83.2±18.6	82.8±19.2	83.4±19.5
Day 1 after PCI (μmol/L)	91.4±18.8 ^a	90.5±17.9 ^a	88.8±19.2 ^{a,c}
Day 2 after PCI (μmol/L)	98.5±20.2 ^b	96.8±19.2 ^b	91.3±18.6 ^{b,c,e}
Day 3 after PCI (μmol/L)	87.6±17.7	86.7±16.8	84.6±17.8
Baseline eGFR (ml/min/1.73m ²)	119.8±5.6	120.4±5.7	121.7±6.4
Day 1 after PCI (ml/min/1.73m ²)	111.3±6.4 ^a	113.2±6.7 ^a	115.7±6.3 ^{a,c}
Day 2 after PCI (ml/min/1.73m ²)	105.4±6.5 ^b	107.5±7.2 ^b	110.1±6.9 ^{b,c,e}
Day 3 after PCI (ml/min/1.73m ²)	117.7±5.9	118.9±6.4	119.2±6.2
eGFR >25% decrease [n (%)]	7 (13.73)	5 (10.2) ^c	4 (8.0) ^d
Incidence of CIN [n (%)]	6 (11.76)	4 (8.16) ^c	3 (6.0) ^d

Notes: ^a: compared to baseline, $P<0.05$; ^b: compared to baseline, $P<0.01$; ^c: compared to basic treatment group, $P<0.05$; ^d: compared to basic treatment group, $P<0.01$; ^e: compared to Standard CS therapy group, $P<0.05$.

Table 3. Changes in urine KIM-1, IL-18 and NGAL

Characteristics	Basic treatment Group (n=51)	Standard CS therapy Group (n=49)	Intensive CS therapy Group (n=50)
Baseline KIM-1 (ng/ml)	0.71±0.06	0.72±0.07	0.71±0.05
Day 1 after PCI KIM-1 (ng/ml)	5.63±0.27 ^a	4.84±0.32 ^a	2.77±0.33 ^{a,b,c}
Baseline IL-18 (ng/L)	42.97±5.82	41.63±4.56	40.35±4.97
Day 1 after PCI IL-18 (ng/L)	62.14±3.53 ^a	55.78±4.17 ^a	46.78±4.33 ^{a,b,c}
Baseline NGAL (ng/ml)	7.97±4.01	7.63±3.77	7.78±3.92
Day 1 after PCI NGAL (ng/ml)	66.53±10.74 ^a	57.13±9.67 ^a	41.66±8.42 ^{a,b,c}

Notes: ^a: compared to baseline, $P<0.05$; ^b: compared to basic treatment group, $P<0.05$; ^c: compared to Standard CS therapy group, $P<0.05$.

there was no significant difference among three groups ($P>0.05$).

Changes in urine KIM-1, IL-18 and NGAL

Within one day after PCI, all urine KIM-1, IL-18, and NGAL levels in patients in the intensive CS therapy group were lower than in those in the standard therapy group and basic treatment group ($P<0.05$) (**Table 3**). There was no significant difference between the basic treatment group and the standard therapy group ($P>0.05$).

Study end points

Overall, CIN occurred in 13 (8.67%) of the 150 patients (**Table 2**). The incidence of CIN in the CS treatment groups is lower compared with the basic treatment group ($P<0.05$); the intensive CS therapy could lower significantly ($P<0.01$).

Compared with the basic treatment group, a lower proportion of patients in the CS treat-

ment groups had an eGFR decrease of 25% or greater ($P<0.05$); patients with an eGFR decrease of 25% or greater accounted for even lower proportion in the intensive CS therapy group and a statistical significance was reached ($P<0.01$, **Table 2**).

Discussion

CIN, a common and potential complication, is defined as a relative increase in the Scr from the baseline value of $\geq 25\%$ or an absolute increase of ≥ 44.2 μmol/L within 3 days after interventional procedure [10]. However, the change of Scr levels fall behind the damage of kidney. Nor can the change demonstrate renal function in time. Recent studies indicate that the values of urine KIM-1, IL-18 and NGAL can early specific to predict the development and progression of CIN [11]. Some other experimental studies suggest that the early decrease in eGFR could be more useful to predict the renal prognosis after angiography [1].

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The pathophysiological mechanism associated with the development of CIN is complex, and remains poorly understood. Renal medullary ischemia following contrast induced intra-renal vasoconstriction, direct cytotoxicity, oxidative tissue damage and apoptosis are possible mechanisms implied for CIN [12, 13]. Many clinical observations have evaluated various agents such as N-acetylcysteine, ascorbic acid, probucol, trimetazidine dihydrochloride, Prostaglandin E1, and statins in effort to identify optimal strategies for reducing the incidence of CIN, but the results are inconsistent [14-18].

The renal impairment caused by CIN belongs to the categories of “Longbi, Nidu, Guange”. Contrast medium can be classified into the TCM category of “hot and humid, medicine poison, blood stasis”. CIN involves the kidney, spleen, lung and other viscera. Triple warmer gasification suffocate is the key to pathogenesis of CIN. The essence of CIN belongs to the scope of deficiency syndrome. The pathogenesis specialty of CIN is deficiency origin and excess in superficiality [19].

CS, an economic traditional Chinese herb, consisting of many amino acids and inorganic elements, can elevate the tolerance of the body to anoxia and ameliorate poor microcirculation. Some basic and clinical studies have proved its efficacy for treating microcirculatory disorders. CS can improve non-alcoholic fatty liver disease in mice by improving microcirculation disturbance, as reported by Li J et al [7]. CS can reduce the renal vascular resistance, ameliorate renal ischemia, increase the renal blood flow, and attenuate the damage of renal microvessels and tissue structure [20]. CS may ameliorate nephrotoxicity-induced renal dysfunction in the rats via antioxidant, anti-apoptosis, and anti-autophagy mechanisms [21]. In addition, by activating super oxide dismutase in renal tissues, CS can scavenge reactive oxygen species and produce antioxidant effects [22]. Another study suggests that supplementation with CS improves exercise performance and might contribute to wellness in healthy older subjects [23]. In recent years, CS has been used to prevent contrast-induced renal impairment. In our previous study, prophylactic treatment with CS in the stable angina pectoris patients undergoing coronary angiography could prevent CIN. The mechanism is that CS can replenish Qi, reinforce the kidney, and

strengthen essence. It can also correct obvious primary deficiency syndrome [24].

There has been little evidence regarding the effects of TCM on CIN so far. A comparatively mature theory system has not been established and needs to be further developed. Therefore, we designed the present study to test the safety and efficacy of CS on the incidence of CIN. CIN occurred in 13 of 150 patients. The incidence of CIN in the CS treatment groups was lower compared with the basic treatment group. In the present study, we select Scr, eGFR, and urine KIM-1, IL-18, NGAL levels after PCI as the index of renal function. Treatment with CS remarkably suppressed the increase in Scr, and urine KIM-1, IL-18, NGAL levels. Meanwhile, the decrease in eGFR levels was delayed. Although our observation of the renal function was only conducted within three days after PCI, a beneficial effect of treatment with CS is highly probable. These results strongly suggest the preventive effect of short-term CS therapy on CIN in ACS patients who were exposed to contrast medium.

Study strengths and limitations

Our study for the first time demonstrated that short-term CS therapy can prevent CIN in patients with ACS undergoing elective PCI. Hence, evidence was provided for TCM prevention and treatment of CIN.

However, the present research also had some limitations. First, the study was only a single-center study with a small sample size, which would have weakened the statistical power of the conclusions. Yet, statistical significance in our study was achieved despite the limited sample. Still, our data need confirmation in future studies. Second, the concerns that the duration of CS uses may be too short to exert its effect for preventing CIN may be raised. However, CS may exert its effect to reduce renal ischemia within 72 hours [20]. Studies that investigated the efficacy of renal protective agent (N-acetylcysteine or ascorbic acid) for preventing CIN also use the methods of short-term use of those drugs [14]. Moreover, the protocol of our study was similar to those of some other studies which were aimed to investigating the short-term effects of medical treatments on the incidence of CIN [25]. Third, in this study, the patients were followed for only 3

days. Some publications have stated that Scr peaked at 3-5 days after administration of the contrast medium and returned to normal within 10 days after. Thus, this study may have missed some peak levels of Scr. However, most patients who experience the CIN usually have their Scr increased within 3 days after contrast administration, and hence most patients with CIN must have been detected in the present study.

Conclusions

These preliminary findings suggest CS significantly reduced the risk of CIN in ACS patients undergoing elective PCI. CS is a protective factor against CIN and intensive CS therapy could be more effective. Therefore, a multiple-center well-designed trial addressing the effect of CS on long-term clinical outcomes is needed before this agent could be added to the armamentarium in the prevention of CIN.

Disclosure of conflict of interest

None.

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