# Effects of hydration combined with Shenfu injection on contrast-induced acute kidney injury in acute coronary syndrome patients undergoing percutaneous coronary intervention

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**Abstract.** The aim of the present study was to evaluate the efficacy and safety of the Shenfu injection (SFI) in the prevention of contrast-induced acute kidney injury (CI-AKI) in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). A single-center prospective and randomized controlled trial was performed and 148 ACS patients undergoing PCI were divided randomly into control (n=74; receiving only 0.9% sodium chloride solution for routine hydration) and intervention (n=74; based upon routine hydration and receiving SFI) groups. Serum creatinine (Scr), blood urea nitrogen and urinary neutrophil gelatinase-associated lipocalin (NGAL) were evaluated at the start, and 1 and 2 days after PCI. Among the 148 patients, 14 (9.4%) experienced CI-AKI subsequent to the procedure. CI-AKI occurred in 2.7% of the SFI group and 16.2% of the control group (P<0.05). The incidence of CI-AKI was lower in the intervention group when compared with the control. No serious adverse effects were observed in all patients. No differences between the levels of Scr and estimated glomerular filtration rate in the two groups were identified. However, 12 h after PCI, the urinary NGAL level in the control group was significantly higher than that in the SFI group (P<0.05). Thus, hydration combined with SFI was identified to be more effective than hydration with sodium chloride in the prevention of CI-AKI in ACS patients undergoing PCI.

## Introduction

With developments in interventional diagnosis and treatment technologies over recent years, an increasing number of patients with coronary artery disease prefer interventional treatment due to its numerous advantages, including the simplicity of surgery, low pain and risk, and fast postoperative recovery compared with conventional surgical therapy (1). Contrast-induced acute kidney injury (CI-AKI) is a major complication when using iodinated contrast media (CM), and has been reported by McCullough and Sandberg (2) to account for a substantial number of hospital-acquired CI-AKI (~11%) with a fatality rate as high as 14% in Michigan, MI, America. The term CI-AKI describes an impairment of renal function, defined as an increase in serum creatinine (Scr) levels by ≥0.5 mg/dl or ≥25% occurring within 3 days following intravascular administration of CM that is not attributable to other causes (3). CI-AKI is among the three major reasons for reduced prognosis of patients following percutaneous coronary intervention (PCI) (4). The morbidity and mortality rates of CI-AKI have increased, particularly in patients with diabetes mellitus and/or chronic kidney disease, and due to this, CI-AKI has become a focus of research in the field (5). However, <30% of patients who undergo PCI typically have diabetes mellitus, and thus have a higher risk of developing CI-AKI than those without diabetes (6). Therefore, the prevention and early detection of CI-AKI are considered to be of utmost clinical importance. In CI-AKI, a reduction in renal perfusion and toxic effects on tubular cells caused by the direct and indirect effects of CM on the kidneys are generally recognized as important mechanisms. Many preventive strategies for reducing the incidence of CI-AKI have been applied, including hydration therapy, withdrawal of diuretics and/or nephrotoxic drugs, and antioxidant and statin treatments (7-10). As a traditional Chinese medicine approach, Shenfu injection (SFI) has been reported to protect renal structure and function against acute renal ischemic-reperfusion injury (11). However, it is unknown whether SFI is effective in reducing CI-AKI in patients with acute coronary syndrome (ACS) undergoing PCI. Therefore, the aim of the present study was to evaluate the protective effects of the SFI combined with hydration therapy for the prevention of CI-AKI in ACS patients after PCI.

## Patients and methods

*Patient population.* A total of 148 ACS patients (92 males and 56 females; aged 66.3±5.9 years) who underwent PCI at the Department of Cardiology of the Affiliated Hospital of

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Xuzhou Medical University (Xuzhou, China), were enrolled over the period between April 2013 and March 2014 and randomly assigned to the SFI group (n =74) or the control group (n=74). The exclusion criteria were as follows: i) Patients that used drugs with renal toxicity during the preoperative period; ii) severe hepatic adrenal dysfunction [severe renal dysfunction was defined as an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 $m^2$]; iii) tumor patients; iv) New York Heart Association class IV (12) congestive heart failure or a left ventricular ejection fraction of <35%; v) thyroid or adrenal dysfunction; and vi) acute or chronic infectious diseases, or hyperpyrexia. Anionic, low osmolar iodinated contrast agent, iohexol (Yangtze River Pharmaceutical Group Co., Ltd., Taizhou, China) was used at the Affiliated Hospital of Xuzhou Medical University. The present study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. Written informed consent was obtained from all participants.

*Methods of intervention*. All patients that had been diagnosed with ACS were enrolled and divided into a control group (receiving antiplatelet, anticoagulation and anti-anginal agents, blood lipids and routine hydration) and a SFI group using a random number table. The SFI group received 40 ml SFI (10 ml per ampoule; Shandong Buchang Pharmaceuticals Co., Ltd., Xian, China) in 250 ml 0.9% sodium chloride solution for routine hydration. The procedure commenced 1 h before coronary angiography and a continuous intravenous infusion was maintained for 4-6 h. Patients with reduced renal function were hydrated with 0.9% saline at 1 ml/kg/h for 12 h before and after catheterization. For emergency coronary interventional procedures, physiological (0.9%) saline was administered intravenously at a rate of 1 ml/kg/h for 12 h following contrast exposure. Venous blood samples (5 ml) were obtained and assessed prior to, and 12, 24 and 48 h after PCI. All Scr levels were measured in a biochemical laboratory of the hospital using an Olympus AU2700 automatic biochemical analyzer (Olympus Corporation, Tokio, Japan). Urine samples were collected prior to, and 12, 24 and 48 h after the procedure and centrifuged 1,409 x g at 4˚C for 20 min. The supernatant fractions were stored at -80˚C until use.

Urinary neutrophil gelatinase-associated lipocalin (NGAL) was measured using an ELISA kit (KHC0061) purchased from R&D Systems, Inc. (Minneapolis, MN, USA). On completion of the assay, the optical density value was read and the standard curve was translated to determine the concentration of NGAL. All the procedures were performed according to the manufacturer's instructions and completed by the same individual.

The eGFR was calculated using a modified Modification of Diet in Renal Disease equation (13) for Chinese patients as follows: GFR (ml/min/1.73 $m^2$) = 175 x Scr $(mg/dl)^{-1.154}$ x age $(years)^{-0.203}$ (x 0.79 if female).

CI-AKI is classically defined as a relative (>25%) or absolute (≥0.5 mg/dl; 44 $\mu$mol/l) increase in Scr from the base line value within the first 72 h following an intravascular CM injection (14).

*Statistical analysis*. Continuous variables are expressed as means ± standard deviation, and categorical data are presented as absolute values and percentages. The t-test and one-way analysis of variance followed by the Scheffe-type multiple comparison test were used for parametric comparison. The Mann-Whitney U test and the Kruskal-Wallis test were performed for nonparametric comparison. The $\chi^2$ test or the Fisher's exact test were conducted to compare categorical variables as required. All hypothesis testing was two tailed. SPSS 16.0 (SPSS, Inc., Chicago, IL, USA) was used to perform the statistical analyses and P<0.05 was considered to indicate a statistically significant difference.

## Results

*General characteristics of the two groups*. Baseline clinical characteristics are presented in Table I. No statistical differences were noted between the groups with respect to age, sex, body mass index, smoking history, drug intake history, risk factors and laboratory examination.

*Changes in Scr, GFR, and urine NGAL values before and after PCI*. Changes in Scr, GFR and urine NGAL values, before and after PCI, are presented in Table II. No significant differences were identified between the levels of Scr and eGFR in the two groups (P>0.05), but 12 h after PCI, the urinary NGAL level in the control group was significantly higher than that in the SFI group (P<0.05).

*Incidence of CI-AKI*. CI-AKI occurred in 2.7% of the SFI group and in 16.2% of the control group, and a significant difference was identified between the two groups (P<0.05).

## Discussion

An increasing number of diagnostic imaging and interventional procedures requires the use of radiographic contrast agents, which has led to a parallel increase in the incidence of CI-AKI. CI-AKI is a serious clinical problem associated with increased morbidity and mortality, particularly in patients with chronic renal failure (3). A key step to safer CI-AKI is to identify patients at risk and subsequently apply proven preventive interventions. Extracellular volume expansion, minimizing the dose of CM, using low-osmolar non-ionic CM and stopping the intake of nephrotoxic drugs have been demonstrated to be effective in reducing CI-AKI.

The predominant mechanism of CI-AKI may be associated with changes of renal hemodynamics and direct toxic effects of contrast agents on tubular epithelial cells. Furthermore, contrast exposure causes a certain degree of imbalance between increased renal vasoconstriction and decreased vasodilatation, leading to a decrease in renal blood flow and contraction of afferent glomerular arteriole, which also involves renal ischemia and cell necrosis (15). In addition, oxygen radicals released by ischemia-reperfusion contribute to renal damage and apoptosis in renal tubular epithelial cells. Additional renal injury may be caused by a decrease in activity of anti-oxidative enzymes and a significant increase of the lipid peroxidation reaction (16).

Currently, hydration is a preventive strategy that has proven useful in the incidence of CI-AKI (17). Various potential mechanisms may contribute to the beneficial effect of hydration, including correct subclinical dehydration, diluting CM, reducing activation of the renin-angiotensin system

Table I. Comparison of clinical characteristics of patients in the two groups.

| Variable | Shenfu group (n=74) | Control group (n=74) | P-value |
|---|---|---|---|
| Age (years) | 68.1±9.1 | 67.6±8.9 | 0.791 |
| Sex (male/female) | 47/27 | 45/29 | 0.735 |
| Current smoker, n (%) | 47 (63.5) | 46 (62.2) | 0.865 |
| Body mass index (kg/m$^2$) | 28.95±2.98 | 28.77±3.01 | 0.52 |
| Hypertension, n (%) | 49 (66.2) | 46 (62.2) | 0.607 |
| Diabetes, n (%) | 26 (35.1) | 27 (36.5) | 0.864 |
| Hypercholesterolemia, n (%) | 14 (18.9) | 15 (20.8) | 0.836 |
| Contrast volume (ml) | 175±36 | 179±39 | 0.731 |
| Hemoglobin (g/dl) | 138±12 | 136±14 | 0.583 |
| Fasting blood glucose (mmol/l) | 6.6±2.0 | 6.4±1.7 | 0.622 |
| Cholesterol (mmol/l) | 4.6±1.4 | 4.8±1.1 | 0.794 |
| Medication | | | |
| Aspirin, n (%) | 72 (97.3) | 70 (94.6) | 0.405 |
| Beta-blocker, n (%) | 63 (85.1) | 65 (87.8) | 0.631 |
| Angiotensin-converting enzyme inhibitor/ angiotensin-receptor blocker, n (%) | 55 (74.3) | 58 (78.4) | 0.562 |
| Calcium channel blocker n (%) | 30 (40.5) | 31 (41.9) | 0.867 |
| Statins | 72 (97.3) | 71 (95.9) | 0.649 |
| Diuretic, n (%) | 14 (18.9) | 15 (20.3) | 0.836 |

Data are expressed as the mean ± standard deviation.

Table II. Comparison the level of Scr, eGFR and urinary NGAL before and after PCI in the two groups.

| Group | Scr ($\mu$mol/l) | eGFR (ml/min/1.73 m$^2$) | Urine NGAL (ng/ml) |
|---|---|---|---|
| Control | | | |
| Pre-PCI | 86.95±23.54 | 84.61±22.15 | 7.25±3.49 |
| Post-PCI (h) | | | |
| 12 | 90.54±19.22 | 82.39±19.30 | 43.75±25.39 |
| 24 | 95.15±18.42 | 83.54±18.35 | 13.69±7.69 |
| 48 | 95.67±19.65 | 82.23±18.45 | 8.79±7.11 |
| Shenfu group | | | |
| Pre-PCI | 92.43±19.35 | 84.55±19.57 | 7.57±5.01 |
| Post-PCI (h) | | | |
| 12 | 90.37±17.69 | 84.73±18.10 | 32.54±24.68[a] |
| 24 | 93.91±20.02 | 87.62±16.41 | 11.422±6.71 |
| 48 | 92.87±19.83 | 83.91±17.54 | 9.44±5.76 |

[a]P<0.05 vs. the same period of the control group. Scr, serum creatinine; eGFR, estimated glomerular filtration rate; NGAL, neutrophil gelatinase-associated lipocalin; PCI, percutaneous coronary intervention.

and tubuloglomerular feedback. In addition, hydration may decrease renal vasoconstriction, increase urine volume and ameliorate blood flow of the renal medulla, thus minimizing reductions in the renal direct toxic effects of contrast agents on tubular epithelial cells caused by CM (18).

The SFI is the extract of Shenfu decoction, and its effective constituents include ginsenoside and aconitine total alkaloids (19). Gu *et al* identified that aconitine was absorbed with no change, while ginsenoside was absorbed after being metabolized by intestinal bacterium, and they were excreted during urination (19). SFI performs numerous pharmacologic actions, which include dilating the coronary artery, improving microcirculation, increasing blood pressure and strengthening myocardial contractility (20-24) Previous studies (25,26) identified that SFI improves vasodilation by increasing nitric oxide generation. Xianyi *et al* (27) indicated that SFI exerts

significant protective effects on ischemia/reperfusion injury of the kidney. In addition, Zheng *et al* (28) identified that SFI markedly decreased the production of malondialdehyde and strengthened the activity of superoxide dismutase on ischemia-reperfusion injury. SFI may inactivate xanthine oxidase directly, remove oxygen free radicals and attenuate the level of lipid peroxidation to protect the kidney (29). Ginsenoside increases selenium levels and glutathione peroxidase activity, alleviates mitochondria swelling and increases the ratio of prostacyclin/thromboxane A2, which may decrease renal vascular resistance, dilate renal arteries, and increase renal blood flow; thus, preventing renal impairment due to hypoxic-ischemia.

Among the 148 patients in the present study, 14 experienced CI-AKI following PCI. CI-AKI occurred in 2.7% of the SFI group and 16.2% of the control group. The increased range and percent age of Scr in the SFI group (n=2) was lower than that in the control group (n=12) of the 14 patients with CI-AKI. At 12 h after the procedure, the urinary NGAL level in the control group was significantly higher than that in the SFI group. Our prospective study identified that the urinary NGAL levels may represent sensitive early biomarkers for CI-AKI compared with Scr, indicating that SFI exerts preferable effects in reducing the incidence of CI-AKI and protecting renal function. NGAL is markedly increased in renal tubular cells, and easy to detect in the plasma and urine of animals with ischemic and nephrotoxic AKI. Previous results have indicated that NGAL is an early molecular marker that reflects AKI and its sensitivity is better than that of Scr (30). The present findings confirm that NGAL levels may be used to identify AKI earlier and more accurately than levels of Scr.

In previous studies, the ophylline/aminophylline, statins and vitamin C were shown to be effective in reducing CI-AKI (31,32). Although the current study indicates that SFI is effective in the treatment of CI-AKI, the findings are based upon small samples. Therefore, randomized, double-blind, multi-centered studies with a larger number of samples are required to confirm the conclusions.

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