Trimetazidine Prevention of Contrast-Induced Nephropathy in Coronary Angiography

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Abstract: *Background:* Contrast-induced nephropathy (CIN) after coronary angiography is frequently observed in patients with chronic renal insufficiency and no effective measures have been developed for prevention of CIN. There is evidence showing that trimetazidine (TMZ) has renoprotective effect on CIN. This study was to evaluate the role of TMZ in the prevention of CIN in renal dysfunction patients undergoing coronary angiography. *Methods:* A total of 132 patients with renal dysfunction who underwent coronary angiography were enrolled in our study and divided into control group (n = 70) and TMZ group (n = 62). Standard hydration was administered in all the patients. In TMZ group, patients were administered TMZ orally for 48 hours before and 24 hours after coronary angiography. Serum creatinine (SCr) and cystatin (CysC) were detected before and after contrast media injection, and the incidence of CIN was evaluated according to the elevation of SCr. Adverse events were observed in 12 months. *Results:* In both groups, CysC and SCr increased significantly after coronary angiography and peaked at 24 and 48 hours, respectively. CysC and SCr were significantly lower in TMZ group than in control group after coronary angiography. The incidence of CIN and adverse events was reduced in TMZ group when compared with control group ($P = 0.034$ and $P = 0.043$, respectively). *Conclusions:* TMZ in combination with standard hydration is more effective than isotonic saline alone in protecting renal function in patients with renal dysfunction who undergo coronary angiography and can reduce the adverse events within 12 months.

Key Indexing Terms: Trimetazidine; Renal dysfunction; Contrast-induced nephropathy; Renoprotection. **[Am J Med Sci 2015;350 (5):398–402.]**

Contrast-induced nephropathy (CIN) is a serious complication after use of iodinated contrast media, especially in high-risk patients with renal dysfunction.[1,2] It is associated with a significantly higher risk for in-hospital and 1-year mortality, even in patients who do not need dialysis. In Mitsuru Abe's study cohort, CIN was significantly correlated with long-term mortality after adjustment in the entire cohort and patients with chronic kidney disease (CKD).[3] Trimetazidine (TMZ) is a cytoprotective, anti-ischemic agent used in the treatment of angina pectoris.[4] TMZ may affect reperfusion at the cellular and mitochondrial levels. In addition, TMZ has a potent antioxidant activity shown in various tissue preparations.[5] On the basis of the anti-ischemic and antioxidant properties of TMZ, Onbasili et al[6] found that TMZ was effective in preventing CIN. Moreover, Rahman et al[7] also found that TMZ could reduce the incidence of CIN. Thereafter, no studies have been conducted to evaluate the protection of TMZ against CIN. TMZ has not been widely used in clinical practice. Thus, it is imperative to its efficacy and safety in clinical practice. This study was to evaluate the role of TMZ in the prevention of CIN in patients with renal dysfunction undergoing coronary angiography or percutaneous coronary intervention (PCI).

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PATIENTS AND METHODS

Patients

A total of 150 patients were enrolled from September 2012 to September 2013. The inclusion criteria were as follows: Patients were 18 to 75 years old, and patients were diagnosed with mild to moderate CKD with an estimated glomerular filtration rate (eGFR) (mL/min×1.73 m^2) between 30 to 89 mL/min×1.73 m^2. The eGFR was calculated from serum samples with the "Cockcroft-Gault" equation[8]: creatinine clearance (mL/min) = ([140–age] × body weight [kg])/(0.818 × SCr [μmol/L]).

Patients were excluded if one of the following items was present: acute renal failure, end-stage renal disease requiring dialysis, unstable renal function, uncontrolled diabetes/hypertension/hyperthyroidism, New York Heart Association class IV congestive heart failure or left ventricular ejection fraction of <35%, acute myocardial infarction requiring primary or rescue coronary intervention, cardiogenic shock, intra-arterial or intravenous administration of iodinated contrast media from 7 days before to 72 hours after administration of agents in this study, any medication to prevent CIN (such as N-acetyl cysteine), or intake of nephrotoxic agents from 24 hours before to 24 hours after administration of agents in this study. Importantly, patients treated with ascorbic acid within 30 days before the study, or those with a known allergy to TMZ were excluded.

Study Protocol

This study protocol was approved by the Ethics Committee of Shanghai Tenth People's Hospital, and all patients provided written informed consent. All patients were fully informed about the study protocol and signed informed consent before study.

This study was a prospective, randomized and controlled clinical trial. Patients were randomly allocated into control group (n = 75) and TMZ group (n = 75). All patients were administered standard hydration[9]: isotonic saline at a rate of 1 to 1.5 mL/kg per hour starting 3 to 12 hours before angiography and up to 12 hours thereafter. Patients in TMZ group were administered TMZ (20 mg) thrice daily orally 48 hours before and 24 hours after coronary angiography. Patients in both groups underwent echocardiographic examination (Vivid 7, GE, Fairfield, CT) before coronary angiography. Ejection fraction of the left ventricle was calculated with Teicholtz formula.

Coronary angiography or PCI was performed through the radial or femoral artery, the arterial stenosis was graded by the Coronary Angiogram Analyzing System II (CAAS II; Pie Medical, Maastricht, the Netherlands).[10] Coronary flow over

the culprit lesion was graded according to the Thrombolysis in Myocardial Infarction trial, and collateral circulation was classified according to the criteria previously reported.[11] Multivessel coronary artery disease was defined as the presence of lesions in 3 or more coronary arteries. The presence of occlusion in major and secondary branches of a coronary artery was defined as single-vessel coronary artery disease. All patients were administered iso-osmolar, nonionic iodixanol (a contrast agent) injection (Visipaque, JX20080286; GE Healthcare, Ireland).

Laboratory Examinations

Blood samples were collected in the morning on the day before and within 3 days after coronary angiography, and the serum creatinine (SCr) and cystatin (CysC) were measured. SCr was measured with the Jaffe method with an auto-analyzing system in the Department of Laboratory Medicine of our hospital. The normal range of SCr is 44 to 97 μmol/L. CIN is defined as the impairment of renal function determined by either a 25% increase in SCr from baseline or 0.5 mg/dL (44 μmol/L) increase in absolute value, within 48 to 72 hours of intravenous contrast administration.[11] CysC was detected by turbidimetric immunoassay with a commercially available kit (Mike Biotechnology Co, Ltd, Sichuan, China). The normal range of CysC is 0.78 to 1.90 mg/L.

Follow-up

The patients' characteristics, medical history, medications, hospital stay and adverse effects of drugs (such as itching, flushing, transitory rash, vomiting, hypotension, bronchospasm and fever) were recorded during hospitalization. During the follow-up period, information was obtained from the patients' medical records or by interviewing patients through telephone or examining patients in outpatient clinics. Major adverse cardiovascular events including cardiac death, nonfatal myocardial infarction and ischemic stroke were recorded. Other adverse events were also recorded, such as end-stage kidney disease, revascularization, coronary artery bypass graft surgery, congestive heart failure or pulmonary edema and need for permanent pacing. The mean follow-up duration was 12 ± 1 month, and the clinicians who were responsible for collecting information during follow-up were blind to grouping in this study.

The end points were the incidence of CIN and adverse events within one year after surgery.

Statistical Analysis

The authors projected the sample size from the study of Onbasili et al,[6] which demonstrated the proportion of patients having an increase in SCr of >0.5 mg/dL 48 hours after administration of contrast agent. The significance level was set at 0.05 and the power at 0.80. The authors calculated that the number of patients required for a TMZ versus control study is 48 per group taking into account the likelihood of incomplete data collection and patients lost to follow up (estimated 20% total). The final number of patients enrolled was 70 and 62 in control and TMZ group, respectively, which is above 0.80. All the data were given as mean ± SD. Clinical and demographic characteristics of patients were compared by Student's *t*-test for continuous variables. Categorical variables were presented as percentages and compared by χ^2 statistics test. Spearman correlation analysis was used to assess the correlation among categorical variables. The Kaplan-Meier method was used to analyze the timing of major adverse cardiovascular events or other adverse events during the follow-up period. A value of 2-sided $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 10.0 for Windows.

RESULTS

Complete laboratory tests were not available in 8 patients (control group: n = 3, TMZ group: n = 5); and 5 patients were lost to follow up (control group: n = 2, TMZ group: n = 3). There were another 4 patients of TMZ group withdrawing from this study for refusing to use TMZ before PCI; and one patient in TMZ group without receiving coronary angiography due to other reasons. The 18 patients mentioned above were excluded from the final analysis. Finally, a total of 132 patients completed the whole study, and the flowchart in the recruitment of these patients is shown in Figure 1.

Baseline Characteristics and Study Population

There were 70 patients in control group and 62 patients in TMZ group. There were no significant differences in neither the age, sex, body mass index, concentrations of hemoglobin, lipid, hypersensitivity C-reactive protein, N-terminal pro-brain natriuretic peptide, eGFR, SCr and CysC on admission, nor in the history of hypertension, diabetes and medications between the 2 groups ($P > 0.05$, Table 1). Significant differences were not observed in angiographic and procedural features, such as contrast agent volume and lesion distribution (Table 2).

SCr and Serum CysC

Preoperative and 72 hours postoperative SCr and CysC concentrations were comparable between the 2 groups. Postoperative SCr concentration was significantly lower in TMZ group at 48 hours than in control group ($P = 0.026$). Baseline SCr significantly increased in 24 hours and 48 hours compared with baseline levels in control group. However, in TMZ group, SCr was not increased at 24 hours but was significantly increased in 48 hours ($P = 0.042$). Postoperative CysC was significantly lower in TMZ group at 24 and 48 hours as compared with control group ($P = 0.000$ and $P = 0.025$, respectively) (Table 3). Baseline CysC significantly increased in 24 hours and 48 hours compared with baseline levels in control group. However, in TMZ group, CysC did not present any increment in 24 hours and 48 hours ($P = 0.235$ and $P = 0.684$, respectively).

Incidence of CIN

CIN was found in 5 patients (8%) in TMZ group who were all belonged to CKD stage 3. In control group, 14 patients

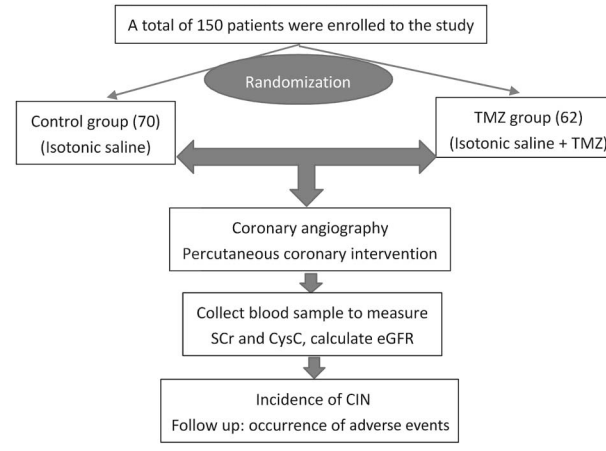

FIGURE 1. Flowchart of the study. CIN, contrast-induced nephropathy; CysC, cystatin; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; TMZ, trimetazidine.