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The effect of trimetazidine on preventing contrast-induced nephropathy after cardiac catheterization

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Abstract

Purpose Trimetazidine has been shown to prevent the risk of contrast-induced nephropathy (CIN) in patients with renal dysfunction undergoing percutaneous coronary intervention (PCI). However, the effect of trimetazidine on CIN in unselected patients is unknown. We aimed to evaluate the effect of trimetazidine on preventing CIN in unselected patients treated with PCI.

Methods 2154 consecutive patients were enrolled and divided into the trimetazidine ($n=529$) and non-trimetazidine group ($n=1625$). Patients in the trimetazidine group received trimetazidine 20 mg thrice daily starting at least 24 h before the procedure and continuing until discharge. The primary outcome was CIN.

Results CIN was observed in 197 (9.2%) patients. The incidence of CIN was similar between two groups (9.1% vs. 9.2%, $P=0.947$). After adjusting for other potential risk factors, trimetazidine did not significantly reduce the risk of CIN (OR = 0.70, 95% CI 0.46–1.08, $P=0.104$). The results remained similar when using the alternate definitions of CIN and different subgroup analysis based on diabetes or chronic kidney disease. In additional, no significant difference between two groups was found with respect to in-hospital major adverse clinical events (1.89% vs. 1.66%, $P>0.05$).

Conclusions Trimetazidine did not exert significant renal protective effect on preventing CIN and in hosptial major adverse clinical events in unselected patients undergoing PCI.

Keywords Trimetazidine · Contrast-induced nephropathy · Percutaneous coronary intervention · Risk factors

Introduction

Contrast-induced nephropathy (CIN), with the reported incidence about 3–14%, is a serious complication after percutaneous coronary intervention (PCI). Nevertheless, it is

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more than 20% in patients with diabetes and chronic kidney disease (CKD) [1–3]. CIN may cause increase in hospital stays, hospitalization expenses, and even adverse cardiovascular events [4, 5].

Various methods for preventing CIN have been investigated in recent years [6, 7]. Trimetazidine (TMZ), a type of myocardial metabolic and anti-ischemic agent, is widely used in patients with coronary disease due to its protective action against free radical damage and ischemia/reperfusion injury [8]. Oxygen-free radical release leading to medullary ischemic injury is a major pathophysiology of CIN. Considering the antioxidant properties and cytoprotective effects of TMZ, several studies have evaluated the effect of TMZ on preventing CIN in patients with CKD undergoing PCI and obtained favorable results [9–13]. However, previous studies had no enough sample sizes and were restricted to only patients with CKD. Few studies have investigated the preventive effect of TMZ on CIN in unselected patients. Therefore, we aimed to assess the effect of TMZ on preventing CIN in patients undergoing PCI.

Methods

Study population

A total of 2154 consecutive patients who underwent cardiac catheterization according to institutional protocol at Guangdong Cardiovascular Institute of Guangdong Provincial People's Hospital, which is the biggest cardiovascular institute in the South-China and the fourth center in China, from March 2013 to October 2015, were prospectively enrolled. Patients with age > 18 years old, and undergoing cardiac catheterization were included. Exclusion criteria were the following: pregnancy, acute myocardial infarction requiring primary PCI, cardiogenic shock, exposure to the CM within the previous 7 days, exposure to nephrotoxic drugs or treatment with medication to prevent CIN and allergy to the contrast medium (CM). In addition, we excluded patients who were undergoing dialysis treatments or had renal transplantation. The TMZ was prescribed at the discretion of the clinicians, and patients were allocated to receive (529 patients; TMZ group) or not receive TMZ (1625 patients; non-TMZ group). Patients in the TMZ group were administered TMZ 20 mg three times daily orally starting 24 h at least before the procedure and continuing to discharge.

The study protocol has sought permission by the ethics committee of Guangdong Provincial People's Hospital, and was performed in accordance with the Declaration of Helsinki. All patients signed written informed consent before the procedure. If consent form could not be signed by patients themselves, it was granted by their next of kin.

Biochemical investigations

Serum creatinine (SCr) levels were measured on the day at hospital admission and days 1, 2, and 3 after the procedure. Blood urine nitrogen, creatine kinase MB, albumin, HbA1c, fasting glucose, and other standard clinical parameters were collected on the morning at hospital admission.

The estimated glomerular filtration rate (eGFR) (mL/min 1.73 m^2) was calculated from Chronic Kidney Disease Epidemiology Collaboration creatinine equation [14]. The left ventricular function (LVEF) in each patient was evaluated by echocardiographic assessment within a 24-h period before the procedure.

Procedure and medications

PCI was performed through the radial or femoral artery following standard clinical practices and techniques. All patients were administered nonionic, low-osmolar CM (either Ultravist® (iopromide) or Iopamiron®, both at 370 mg/mL). Hydration with intravenous normal saline (0.9%) at a rate of 1 mL/kg/h was initiated during the procedure and continued for 6–12 h after CM exposure. However, if the patient's LVEF was less than 40%, the hydration rate was decreased to 0.5 mL/kg/h. All eligible patients received aspirin (300-mg loading dose before PCI, thereafter 100 mg/day) and clopidogrel (300-mg loading dose before PCI, thereafter 75 mg/day). In addition, antiplatelet agents (aspirin/clopidogrel), diuretics, β-blockers, and angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors were given to patients in both groups following the clinical protocols according to interventional guidelines.

Clinical outcomes

The primary outcome was CIN. CIN was defined as the impairment of renal function as determined by either an absolute increase in SCr > 0.5 mg/dL (44.2 mmol/L) or a 25% relative increase over the baseline values within 48–72 h of intravenous contrast administration (CIN total) [15]. The other definitions of CIN included: (1) an absolute increase in SCr > 0.5 mg/dL within 48–72 h (CIN 44.2); (2) 25% relative increase from baseline within 48 h (CIN 25%). The secondary end point was the occurrence of major adverse clinical events (MACE), which included all-cause mortality, renal replacement therapy, relapse of myocardial infarction, stroke and target vessel revascularization during hospitalization.

Statistical analysis

SPSS version 20.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. Continuous variables are presented as

mean ± standard deviation (SD) or medians. The analysis of continuous variables was conducted by Student's *t* test or the Wilcoxon rank sum test (if not normally distributed). Categorical variables were presented as percentages and compared by Pearson Chi square test or Fisher's exact test. Variables that were significant in the univariate analysis or clinically important were included in the multivariable models. In addition, subgroup analyses were conducted for the incidences of CIN. A value of two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the study patients

The overall analysis contained 2154 patients (529 for TMZ group and 1625 for non-TMZ group). The mean age between two groups was 64.21 ± 10.79 vs. 62.61 ± 10.58 years ($P = 0.003$). The eGFR levels and LVEF% on admission were sligthly higer in non-TMZ groups ($P < 0.05$). There was no significant difference in gender and medical history, including hypertension, diabetes, smoking, and prior MI between the two groups. The TMZ group showed significantly higher levels of uric acid than the non-TMZ group ($P = 0.037$); however, significant differences were not observed in other laboratory findings such as total cholesterol (all $P > 0.05$). There were neither significant differences in CM volumes used (TMZ group 115.87 ± 64.06 mL vs. non-TMZ group 113.64 ± 65.03 mL, $P = 0.491$) nor intake of medication (except for diuretic, $P = 0.011$) during hospital stay ($P > 0.05$, Table 1).

The effect of TMZ on incidence of CIN and in-hospital outcomes

Prevalence of CIN was not significantly different between TMZ and the non-TMZ groups (9.1% vs. 9.2%; $P = 0.947$); similar proportions in both groups were also observed, respectively, on the basis of the alternate CIN definitions (Fig. 1). In addition, the occurrence of in-hospital MACE, including all-cause mortality (0.9% vs. 0.4%, $P = 0.106$), target vessel revascularization (0% vs. 0.6%, $P = 0.184$), stroke (0.2% vs. 0.2%, $P = 0.984$), relapse of myocardial infarction (0.4% vs. 0.1%, $P = 0.237$) and requiring renal replacement therapy (0.2% vs. 0.4%, $P = 0.427$) were similar between the two groups (Table 2).

Pretreatment with TMZ had a similar effect as non-TMZ pretreatment on the incidence of CIN (OR = 0.70, 95% CI 0.46–1.08, $P = 0.104$), after adjusting for other potential risk factors (Table 3). In addition, similar results were also shown for the alternate definitions of CIN (Table 3). Furthermore, subgroup analysis among patients with diabetes or stage of CKD demonstrated no significant difference in the risk of CIN with TMZ pretreatment according to any of the three definitions of CIN among these patients (Supplementary Table S1).

Discussion

The present study showed that TMZ did not significantly decrease the risk of CIN and in hospital MACE in unselected patients undergoing PCI, even based on the alternate CIN definitions and different subgroup analyses.

Although the mechanism of CIN remains unclear, some scholars believe that renal medullary ischemia, vasoconstriction and oxygen-free radical injury from contrast agents play a major role in the pathogenesis [16, 17]. However, there is no effective approach except for hydration for CIN prevention at present.

Growing clinical evidence showed treatment benefits of TMZ to patients with myocardial ischemic conditions in terms of major cardiac events, myocardial damage and reduction of reperfusion injury [18, 19]. These studies were based on the concept that TMZ was associated with a direct anti-ischemic effect while decreasing production of free oxygen radicals, calcium and acid accumulation. The cytoprotective properties of TMZ in renal tissue also resulted in numerous trials to evaluate its potential effect on the prevention of CIN and prognosis. Rahman et al. found that in patients with raised SCr levels, the group using TMZ had a significantly lower incidence of CIN than those without TMZ (4% vs. 14%, $P < 0.05$) [12]. Similar results were obtained by Onbasili et al. including 82 patients with high SCr levels and showed a lower risk of CIN in the TMZ group than control group (2.5% vs. 16.6%, $P < 0.05$) [20]. In addition, Liu et al. showed that TMZ plus standard hydration both could protect renal function (8% vs. 20%, $P = 0.034$) and reduce the adverse events (9.6% vs. 22.8%, $P = 0.043$) within 12 months in patients with renal dysfunction [13]. Moreover, similar findings have been reported from studies that targeted patients with diabetes mellitus and mild-to-moderate CKD undergoing PCI [21, 22]. It is noteworthy that the patients enrolled in these studies were complicated with impaired renal function with/without diabetes mellitus.

However, the results in the present study were different from those of previous studies and the reasons may be as follows: First, our study was not strictly specific to populations with CKD or diabetes mellitus. As it is known, patients with CKD or diabetes mellitus are independent risk factors for CIN. More attention and caution would be given in such populations. Therefore, the reducing incidence of CIN in these patients may be not absolutely contributed to TMZ. In addition, researchers in several previous studies [12, 20, 21] arrived at this conclusion by administering

Table 1 Baseline demographic and clinical characteristics of patients with or without trimetazidine pretreatment

Variables	TMZ group ($n=529$)	Non-TMZ group ($n=1625$)	*P* value
Age (years)	64.21 ± 10.79	62.61 ± 10.58	0.003
Age > 75 years, *n* (%)	108 (20.4)	236 (14.5)	0.001
Female, *n* (%)	124 (23.4)	412 (25.4)	0.377
SBP (mmHg)	129 ± 19	130 ± 33	0.376
DBP (mmHg)	76 ± 12	77 ± 12	0.031
Hypertension, *n* (%)	299 (56.5)	932 (57.4)	0.737
Diabetes, *n* (%)	126 (23.8)	387 (23.8)	0.999
Smoking, *n* (%)	187 (35.3)	601 (37.0)	0.498
Prior MI, *n* (%)	58 (11.0)	162 (10.0)	0.512
CABG, *n* (%)	10 (1.9)	7 (0.4)	0.001
Total cholesterol (mmol/L)	4.29 ± 1.11	4.41 ± 1.46	0.115
LDL-C (mg/dL)	2.53 ± 0.87	2.61 ± 0.93	0.107
Uric acid (umol/L)	390.78 ± 116.73	378.33 ± 101.45	0.037
hs-CRP (mg/L) (median)	3.34	2.85	0.525
HbA1c (%)	6.49 ± 1.27	6.54 ± 1.97	0.618
Serum albumin (g/L)	35.38 ± 4.54	35.73 ± 4.32	0.124
Hemoglobin (g/L)	134.07 ± 16.45	134.40 ± 16.36	0.844
eGFR (mL/min/1.73 $m^{2)}$	78.54 ± 20.02	80.89 ± 19.50	0.017
LVEF% on admission (%)	58.11 ± 13.56	59.98 ± 11.80	0.005
Contrast volume (mL)	115.87 ± 64.06	113.64 ± 65.03	0.491
Number of stents (*n*)	1	1	0.678
Length of stent (mm)	35.09 ± 32.36	33.5 ± 32.32	0.369
Statins, *n* (%)	501 (94.7)	1539 (94.7)	1.000
ACEI/ARB, *n* (%)	452 (85.3)	1429 (87.9)	0.108
Calcium channel blocker, *n* (%)	99 (18.7)	269 (16.6)	0.251
Diuretic, *n* (%)	90 (17.0)	205 (12.6)	0.011
β-Blocker, *n* (%)	462 (87.3)	1431 (88.1)	0.656

SBP systolic blood pressure, *DBP* diastolic blood pressure, *MI* myocardial infarction, *CABG* coronary artery bypass grafting, *LDL-C* low-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *HbA1c* hemoglobin A1c, *eGFR* estimated glomerular filtration rate, *LVEF* left ventricular ejection fraction, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

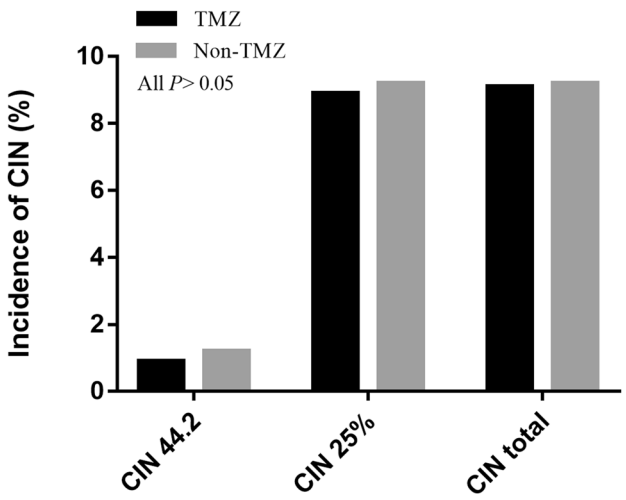

Fig. 1 Incidence of contrast-induced nephropathy in patients with/without trimetazidine

Table 2 In-hospital outcomes in patients with or without trimetazidine pretreatment

Variables	TMZ group ($n=529$)	Non-TMZ group ($n=1625$)	*P* value
All-cause mortality (%)	5 (0.9)	6 (0.4)	0.106
Target vessel revascularization (%)	0 (0)	9 (0.6)	0.184
Stroke (%)	1 (0.2)	3 (0.2)	0.984
Re-myocardial infarction (%)	2 (0.4)	2 (0.1)	0.237
Renal replacement therapy (%)	1 (0.2)	7 (0.4)	0.427

TMZ in conjunction with normal saline + N-acetylcysteine instead of including a treatment arm of trimetazidine alone. N-acetylcysteine was considered to be a scavenger of reactive oxygen species with the potential to prevent CIN [6, 23]. Thus, the conclusions drawn could be attributed to the combination of TMZ and *N*-acetylcysteine. On the contrary, the

Table 3 Multivariate analysis of risk factors for contrast-induced nephropathy

CIN definitions	Variables	Multivariate analysis		
		OR	95% CI	*P* value
CIN total	Trimetazidine	0.70	0.46–1.08	0.104
	Age > 65 years	1.21	0.83–1.76	0.326
	Male vs. female	0.95	0.67–1.34	0.757
	Diabetes	0.99	0.89–1.09	0.796
	Uric acid	1.00	1.00–1.00	0.444
	Hypertension	1.38	0.95–2.02	0.093
	LVEF%	1.00	0.98–1.01	0.536
	eGFR ≤ 60	0.88	0.52–1.47	0.618
	CM volumes > 100 mL	1.24	0.87–1.78	0.239
	Diuretic	1.86	1.21–2.88	0.005
CIN 25%[a]	Trimetazidine	0.69	0.44–1.07	0.098
CIN 44.2[a]	Trimetazidine	0.26	0.06–1.18	0.081

CIN contrast-induced nephropathy, *LVEF* left ventricular ejection fraction, *CM* contrast medium, *eGFR* estimated glomerular filtration rate (mL/min/1.73 m^2)

[a]Adjusting the same potential risk factor with CIN total

present study excluded the patients treated with medication to prevent CIN (e.g., *N*-acetylcysteine, sodium bicarbonate), which could remove such interference. Moreover, the largest sample size among previous studies was 200 patients in each arm [12]. Nevertheless, this would be not adequate to draw a more credible conclusion. Accordingly, more than 2000 patients were included in the present study to help add more evidence to physicians' clinical practice. Finally, alternate CIN definitions and different subgroup analyses were performed to evaluate the effect of TMZ, which may be different from the focus of previous studies.

Limitations

There were several limitations which should be taken into consideration. Firstly, this was a single-center, prospective and observational study to which causality cannot be ascribed. Secondly, consistent with previous studies, this study did not further investigate the effect of different doses and treatment regimens on outcomes. However, the dosage of TMZ used in the present study was almost equal to previous studies. Thirdly, though cystatin C is more sensitive and responds faster than SCr in the incidence of CIN, we did not use this biomarker. Fourthly, the present study did not further evaluate the preventive effect of TMZ on long-term mortality and MACE because the present study focused on the risk of in-hospital development of CIN. Finally, further randomized control trials with large sample size are needed to demonstrate the role of TMZ in unselected patients undergoing cardiac catheterization.

Conclusion

In conclusion, TMZ did not exert a significant renal protective effect on preventing CIN and in hospital MACE in unselected patients undergoing coronary angiography or PCI.

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Compliance with ethical standards

Conflict of interest The authors of the present manuscript have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional.

Informed consent Informed consent was obtained from all individual participants included in the study.

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