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Chronic treatment with trimetazidine after discharge reduces the incidence of restenosis in patients who received coronary stent implantation: A 1-year prospective follow-up study

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ABSTRACT

Background: The incidence of stent restenosis (SR) has risen with as more patients are being treated with drug-eluting stents (DESs). Trimetazidine has multiple favorable effects on the cardiovascular system. Here, we aimed to evaluate whether chronic treatment with trimetazidine reduced the incidence of SR.
Methods: From January 2009 to December 2011 at Chinese PLA General Hospital, 768 patients were enrolled and randomized into the trimetazidine treatment group (TG, n = 384) and control group (CG, n = 384). After DES implantation, all patients were treated with regular medication. In the TG, trimetazidine was administrated at 20 mg tid for at least 30 days. All patients received follow-up angiography 9–13 months after discharge. Major adverse cardiac and cerebrovascular events (MACCEs) were recorded.
Results: Six hundred thirty-five patients were included in the final analysis (TG, n = 312; CG, n = 323). SR occurred in 49 (7.7%) patients. The TG had a lower incidence of SR compared to the CG (4.2% vs. 11.1%, $p = 0.001$). At the 30-day follow-up, the TG exhibited a higher left ventricular ejection fraction than the CG (65.4 ± 10.7 vs. 63.1 ± 10.4, $p = 0.006$). The incidence of MACCEs was also lower in the TG at the 1-year follow-up (6.1% vs. 10.8%, $p = 0.032$). Further multivariate analysis revealed that trimetazidine treatment was a predictor for SR (OR: 0.376; 95% CI: 0.196–0.721; $p = 0.003$).
Conclusions: Trimetazidine treatment effectively reduced the incidence of SR and MACCEs after DES implantation at the 1-year follow-up.

1. Introduction

In the bare-metal stents (BMSs) era, the stent restenosis (SR) occurred in approximately 25% of patients with BMS implantation [1,2]; this incidence decreased to around 3.6%–10% after the introduction of drug-eluting stents (DESs) due to the significant inhibitory effect of eluting drugs on the proliferation of smooth muscle cells [3–6]. Despite the low incidence of stent restenosis, in clinical practice, we lack useful and accurate methods to identify which patients are at high risk of repeat revascularization. Based on this, we aimed to identify effective methods to further decrease the incidence of SR in DES patients.

Previous studies have suggested that SR is associated with several factors, including biological, mechanical, and technical factors, and that the main pathophysiological process involved in restenosis is the proliferation and migration of smooth muscle cells [7–10]. Endothelial dysfunction (ED) also contributes to restenosis, as demonstrated by many clinical studies [11–14], and impaired flow-mediated dilation (FMD) in the brachial artery, an indicator of ED, is associated with late SR in patients undergoing percutaneous coronary intervention (PCI) [15,16].

Trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride, TMZ) has been used to alleviate myocardial ischemia through multiple mechanisms [17–21]. Studies have also demonstrated that TMZ can improve ED and has a favorable influence on nitric oxide-dependent preservation of the endothelial barrier [22,23]. Based on these findings, in the present study, we investigated whether TMZ could inhibit the occurrence and progression of SR in patients with DES implantation, which may be helpful to improve the overall prognosis of patients with coronary heart disease.

2. Material and methods

2.1. Study population

From January 2009 to December 2011 at the Chinese PLA General Hospital, patients undergoing PCI for the first time were enrolled in this study. All PCIs were performed at the Catheterization Laboratory at the Chinese PLA General Hospital. DESs were implanted in all patients.

Patients were enrolled and randomly assigned to the TMZ treatment group (TG) or control group (CG) according to the following criteria: clinical indication of percutaneous coronary revascularization, age ≥ 18 years, de novo severe stenosis in a native coronary

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artery, lesion suitable for stent, reference vessel size between 2.5 and 4.0 mm by visual estimation, and DES (sirolimus or paclitaxel) implantation only. Exclusion criteria included the following: acute myocardial infarction within 2 weeks before PCI and other contraindications to treatment with TMZ, bypass restenosis, intolerance of platelet inhibitors and statins, impaired liver function (alanine aminotransferase [ALT] 2-fold above upper normal limits), renal insufficiency requiring hemodialysis, pregnancy, connective tissue disease, life expectancy ≤ 12 months, and inability to complete at least a 1-year follow-up. Acute myocardial infarction was defined according to two guidelines [24,25].

This study was approved by the Ethics Committee of the Chinese PLA General Hospital, and all patients gave their written informed consent before TMZ treatment. The study was conducted according to the principles of the Declaration of Helsinki, 2008 version.

2.2. PCI and stent implantation

PCIs were performed using standard techniques by experienced cardiologists who were blinded to this study, and DESs (sirolimus or paclitaxel) were implanted in all patients via the right (or left) femoral (or radial) artery. The ratio of stent diameter to distal reference vessel diameter was 1:1 to 1.1:1, and the pressure of stent delivery was at least 13 atm. The available stent lengths were 13–38 mm, and the stent diameters were 2.5, 3.0, 3.5, and 4.0 mm.

2.3. Randomization, medication, and follow-up

Before PCI, aspirin was administered to each patient at a loading dose of 300 mg, and clopidogrel was administered at 300 mg. After PCI, all patients received standard medication treatment, including double antiplatelet therapy (aspirin at 100 mg/day, indefinitely, and clopidogrel was administered at 75 mg/day for at least 1 year), statins of different doses indefinitely, and other drugs if necessary. When confirmed to be stable, all eligible patients were randomly assigned immediately after the PCI to either the CG or TG. In the TG, patients received a loading dose of 60 mg TMZ the same day after PCI, followed by 20 mg TMZ 3 times a day for at least 1 month at discharge. Patients in the CG did not receive either a placebo or additional therapy. Before TMZ treatment and 1 month after discharge, red and white blood cells, platelet counts, and serum levels of K^+, Na^+, ALT, creatinine, cholesterol, and triglycerides were tested. A clinical interview was required at the end of 1, 3, 6, 9, and 12 months after PCI. Major adverse cardiac and cerebrovascular events (MACCEs, including: death from any cause, nonfatal myocardial infarction, revascularization, stroke, and cerebral bleeding) over the duration of follow-up were recorded. Coronary angiography was applied 9–13 months after the initial PCI procedure or earlier if necessary. Angiographic restenosis was defined as 50% or more luminal narrowing at follow-up angiography and was classified as summarized by Mehran et al. [26]. Echocardiography was performed by independent doctors who were blinded to this study.

The primary end point of this study was angiographic restenosis, defined as diameter stenosis of 50% or more in the target lesion during follow-up angiography. In patients with more than one stent, restenosis were counted separately. MACCEs were identified as secondary end points [27].

2.4. Statistical analysis

The sample size of the study was determined on the basis of a test for trend analysis based on the estimation for the primary end point of angiographic restenosis and late loss according to our previous observations and from recent trials with DESs; in the CG, we assumed an incidence of restenosis of 12% in accordance with recently reported data and our observations of in-segment restenosis with DESs. In the TG, we assumed a restenosis rate of 5% according to other studies assessing preventive methods for restenosis. Using a two-sided test for differences in independent binomial proportions with an α level of 0.05 and a β level of 0.2, we calculated that 492 patients (246 for each group) would have to undergo randomization for this study; thus, until December 31, 2011, we enrolled a total of 384 patients in each arm for randomization.

Continuous variables were expressed as the mean ± standard deviation (SD) and compared using an unpaired two-sided Student's *t*-test when normal distribution and equal dispersion were confirmed. The Mann–Whitney *U* test and the Wilcoxon's signed-rank test were used when the variance was unequal. Categorical variables were expressed as percentages (%) and compared using X^2 analysis or Fisher's exact test if necessary. Freedom from primary and secondary end points at follow-up were analyzed by Kaplan–Meier survival curves and compared by log-rank test. A multiple logistic regression analysis, the backward stepwise method (Wald), was performed to correlate angiographic restenosis with clinical and angiographic variables, including treatment groups. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS (version 17.0 for Windows, SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

From January 2009 to December 2011, a total of 3766 patients with coronary heart diseases (including stable angina, unstable angina, and acute myocardial infarction) received PCI with DES implantation at the same time at our hospital. Among these patients, 768 patients were randomly assigned to the TG or CG according to the inclusion criteria, and 2998 patients were excluded according to the exclusion criteria. At the end of this study, 72 patients in the TG and 61 patients in the CG were excluded for various reasons, and the remaining 635 patients (TG, n = 312; CG, n = 323) were included in the final analysis (Fig. 1). The baseline demographic, clinical, and angiographic characteristics of the patients in the 2 groups were generally well balanced (Table 1,2). In the final analysis population, a total of 1143 stents were inserted: 532 in the TG and 611 in the CG; small stents (2.5 mm) were used in 29.1% of lesions. General information of stents used in the TG and CG were also balanced.

3.2. Clinical and angiographic follow-up

In the final analysis, all 635 patients received 11.4–12.6 month (11.9 ± 1.8) follow-up. There were no differences in in-hospital events or 30-day follow-up events between the TG and CG ($p < 0.001$). During the entire follow-up period of 11–13 months after discharge from hospital, MACCEs occurred in 19 patients in the TG and 35 patients in the CG. During the course of treatment with TMZ, none of patients in the TG had TMZ-associated side effects (Table 3).

Survival curves of freedom from MACCEs in the TG and CG are shown in Fig. 2A ($p = 0.034$). Survival analysis revealed that patients in the TG had significantly better outcomes, with a 43.5% reduction in total MACCEs compared to patients in the CG. Echocardiography at the 30-day follow-up demonstrated that the average ejection fraction in the TG was higher compared with that in the CG (65.4 ± 10.7 vs. 63.1 ± 10.4, $p = 0.006$, Fig. 2B).

Repeated angiography at follow-up revealed 49 patients (7.7% of 635 patients) with restenosis, of which 13 (4.2%) patients were in the TG, while 36 (11.1%) patients were in the CG. This result suggested that TMZ treatment reduced SR by 62.2% compared to no treatment.

3.3. Predictors for ISR at 1 year after PCI

In Table 4, we summarize the clinical, lesional, and procedural characteristics in patients with or without restenosis. From these parameters, we selected traditional factors, such as age, diabetes mellitus, hypertension, current smoking, systolic blood pressure (SBP), and other factors with *p*-values of less than 0.1 (mean stent length, mean stent diameter, and TMZ treatment) as variables entered into the logistic regression model to identify their relationship with restenosis. The results are shown in Table 5. TMZ treatment was associated with a low incidence of SR after PCI (OR: 0.376, 95% CI: 0.196–0.721, $p = 0.003$). Similar to the results of other studies, we found that age, diabetes mellitus, current smoking, mean stent length, and mean stent diameter were also associated with SR. These results suggested that the relationships of SR with hypertension and SBP were both not statistically significant ($p = 0.080$ and 0.076, respectively).

4. Discussion

In this study, we demonstrated for the first time that TMZ therapy for 30 days after stent implantation at discharge could significantly reduce the incidence of SR in patients with coronary heart disease. Moreover, treatment with TMZ was also associated with a reduction in MACCEs after DES implantation at the 1 year follow-up. Echocardiography at the 30-day follow-up exam revealed a higher left ventricular ejection fraction in the TG than in the CG. These results were consistent with the results of other studies [28–33].

The proliferation and migration of vascular smooth muscle cells have been recognized to be the main pathophysiological processes involved in SR [9,10]. Therefore, drugs with the potential to inhibit SMC proliferation and migration may be used therapeutically to reduce SR. Fortunately, TMZ also has an inhibitory effect on the proliferation and