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Intra-Coronary Administration of Tacrolimus Prior to First-Balloon Inflation Attenuates Infarct Size and Improves Left Ventricular Function in Patients with ST-segment Elevation Myocardial Infarction (COAT-STEMI) Undergoing Primary Coronary Intervention

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Abstract

Background: and phenomenon which occurred frequently during primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) caused unfavorable prognostic outcomes. Currently, no effectively therapeutic strategy to prevent this phenomenon.

Objectives/Design: To evaluate the and safety of intra-Coronary Administration of Tacrolimus prior to

Methods/Results of Pilot Study: Twenty-nine STEMI patients (group 1) were prospectively administered tacrolimus (2.5 mg intra-coronary slow injection using thrombuster) prior to A historical-control group (group 2) was chosen from consecutive patients undergoing primary PCI just prior to the pilot study. Age, gender, CAD-risk factors, peak CK-BM, and baseline left-ventricular performance were not different between groups 1 and 2 (all p>0.1). Chest pain onset-to-door and door-to-balloon times, mean Killip score upon presentation, number of multi-vessel disease, pre-PCI TIMI and 30-day death were similar between these two groups (all p>0.1). The incidences of advanced CHF (≥ NYHA 3) and pulmonary edema were higher in group 2 than in group 1, whereas the incidence of anterior-wall infarction, TIMI-3 and 90 minute ST-segment-resolution rate showed an opposite pattern of advanced CHF between these two groups. The incidence of myocardial blushing grade was higher in group 2 than in group 1 (p=0.034).

Conclusion: Tacrolimus therapy shows promise as a safe and effective therapeutic agent for STEMI. The positive preliminary outcomes from this pilot study suggests randomized-controlled trials are now required to evaluate the effectiveness and safety of Tacrolimus for STEMI patients. (clinical trials no: ISRCTN38455499).

Keywords: Tacrolimus; ST-segment elevation myocardial infarction; Primary percutaneous coronary intervention; Myocardial blushing grade; ST-segment resolution.

Introduction

The development of pump failure depends on the severity of myocardial ischemia and extent of necrosis after Acute Myocardial Infarction (AMI) [1-9]. Therefore, minimizing myocardial damage and preservation of the viability of at-risk myocardium are important approaches to post-infarct care [10-13].

To achieve these goals, reperfusion through Percutaneous Coronary Intervention (PCI) [11-13], thrombolysis [14-15], together with pharmacomodulation [10,11] have become the current standards for the treatment of ST-segment elevation myocardial infarction (STEMI). Regarding the mechanisms underlying the slow-flow and no-reflow phenomena after primary PCI, previous studies have identified the timely reperfusion [12], the burdens of thrombosis and plaque content as well as ischemia-reperfusion (IR) injury as the principal contributors [16-18]. IR injury, in particular, has been further demonstrated to be associated with inflammation that aggravates myocardial damage even after successful reperfusion [17,19,20]. Indeed, a number of recent studies have attributed myocardial damage after AMI to inflammation [21-26] that is promptly elicited by tissue damage and necrosis [17,19-26]. In this regard, it is rational to believe that innate immune response [21,22,27] followed by activated adaptive immune signaling [21,27] may play key roles in the regulation of inflammatory reaction after AMI, especially at the early stage of AMI. Therefore, beside reperfusion therapy, early inhibition of the propagations of inflammatory reactions and immune signaling may be of utmost importance in suppressing the progression of myocardial damage after AMI.

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Our recent experimental studies have revealed that tacrolimus treatment effectively attenuated inflammatory and immune reaction, limited infarct size, and preserved LV function [28-30]. In view of the fact that immune and inflammatory reactions are major contributors to death of cardiomyocytes after AMI [21-33,42,43] and that tacrolimus is a potent immunosuppressant, we hypothesized that adjunctive tacrolimus therapy during primary PCI might increase final TIMI-3 flow and myocardial blushing grades, limit the extent of myocardial infarction, and improve LV function in patients with STEMI. Based on this hypothesis, we propose to conduct the intra-COronary **A**dministration of **T**acrolimus (COAT-STEMI) trial prior to first-balloon inflation to investigate the impact of intra-coronary administration of tacrolimus on reperfusion rate, LV function, and clinical outcome in patients with STEMI undergoing primary percutaneous coronary intervention (primary PCI). Prior to enrollment of patients for the COAT-STEMI trial, a single site, prospective, non-blinded pilot study has been finished

Materials and Methods

Study design

This pilot study protocol has been approved by the institutional review boards of Chang Gung Memorial Hospital. Written informed consent was obtained from all study participants prior to enrollment. The IRB number of this pilot study is 103-0873B. The primary objectives include to evaluate the safety, procedural success rate, i.e., final TIMI-3 flow (achievement of normal blood flow) in IRA and efficacy of treatment (myocardial blushing grade ≥ 2 and 90 minute ST-resolution rate). The secondary objectives vof this study were 30 day combined endpoint of recurrent MI or death.

Rationale for this pilot study

The objective of this pilot study was to generate initial prospective data on the concept that tacrolimus-treated STEMI patients might have better final TIMI-3 flow, MB grade and 90 minute resolution of ST-segment elevation when compared with that of historical control subjects. Of particular important was that treatment procedure safety was assessed in the pilot study.

Study patients, ethics, enrollment period, inclusion and exclusion criteria

According to the current treatment program at our hospital, all patients with acute STEMI with onset of chest pain <12 hours are eligible for primary PCI. According to the protocol of this pilot study, consecutive patients (age between ≥ 20 and ≤ 80 year old) with STEMI undergoing primary PCI were be prospectively enrolled. All enrolled patients received tacrolimus treatment (treated by 2.5 mg of tacrolimus by intra-coronary injection) prior to first balloon inflation. This research protocol had been approved by the institutional review boards of each trial center.

Study exclusion criteria include patients who had history of coronary artery bypass surgery, age >80 year old, occurrence of recent AMI or stroke in less than three months, history of tacrolimus allergy or use of immunosuppressant therapy, cardiogenic shock, infection and active inflammatory conditions, pregnancy or breastfeeding, liver cirrhosis, recipient of organ transplantation, hemodialysis, conditions with life expectancy estimated to be less than one year, cancer, patients still participating in other clinical trial, and those who refused to participate in the study.

Between August 2013 and January 2014, 29 patients who had fit the criteria were prospectively enrolled into the pilot study. Between February 2013 and July 2013, 52 consecutive patients were enrolled to serve as the historical control group.

Procedure and protocol for primary PCI and study treatment

Primary PCI was performed according to a standard protocol as previously described [3,4,12,16,33]. A transradial artery approach using a 6-French arterial sheath and a 6-French guiding catheter is a routine procedure for acute STEMI at our hospital unless Allen's test was positive on both hands. After the guiding catheter engaged the Infarct-Related Artery (IRA), the guide wire crossed the lesion and advanced into the distal part of the IRA. The thrombuster (Terumo Co.) was tracked along the guide wire to cross the obstructive lesion. Tacrolimus (Astellas Taiwan, Fujisawa Ireland Co., Ltd. Killorglin Co. Kerry, Ireland) with a dose of 2.5 mg in 0.5 cc volume was mixed with 200 mg of nitroglycerine in 2.0 cc and 2.5 cc normal saline, followed by slow injection through the thrombuster catheter to the IRA. Balloon dilatation and stenting was then be proceeded 3 minutes after intra-coronary injection of tacrolimus.

Intra-aortic balloon pump (IABP) support was inserted via femoral arterial approach in patients with acute pulmonary edema associated with unpredictable unstable condition or hemodynamic instability during primary PCI.

Oral medications

Patients received a loading dose of clopidogrel (600 mg orally) in the Emergency Room, followed by a maintenance dose (75 mg once daily) for at least 12 months, or a loading dose of ticagrelor (180 mg orally), followed by a maintenance dose (90 mg twice daily) for at least 12 months after primary PCI. In addition, they received a loading dose of aspirin (325 mg orally), followed by a maintenance dose (100 mg daily). Other commonly prescribed medications also included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, beta-blockers, isosorbide mononitrate and diuretics.

Definitions

STEMI was defined as 1) typical chest pain lasting for more than 30 minutes with ST-segment elevation >1 mm in at least two consecutive precordial or inferior leads, or 2) typical chest pain lasting for more than 30 minutes with a new-onset complete left bundle branch block. Procedural success was defined as a reduction to residual stenosis of <20% by balloon angioplasty or successful stent deployment at the desired position with a residual stenosis <10% followed by TIMI grade 3 flow in the IRA. Multi-vessel disease was defined as stenosis of ≥ 50% in ≥ 2 major epicardial coronary arteries.

Definition of TIMI flow, myocardial blushing and 90-minute ST-resolution

Assessment of the TIMI flow grade and myocardial blushing (MB) grade followed previous reports [34,35]. In addition, measurement of 90 minute ST-resolution using complete electrocardiogram was based on the criteria as described recently [36,37]. Furthermore, two expert interventional cardiologists who were blinded to the treatment allocation assessed the angiographic findings and 90 minute ST-resolution results.

Echocardiography measurement

Conventional echocardiography with digital images acquired by standard 2-dimenional views, M-mode and color Doppler assessment was collected according to the standardized protocol.

Statistical analysis for pilot study results

Data were expressed as means ± SD or percentage of patients where appropriate. The clinical and laboratory data were analyzed and comparisons were done using independent *t* test for continuous variables and Fisher's exact or chi-square test for categorical variables. Statistical analysis was performed using SPSS statistical software for Windows version 13 (SPSS for Windows, version 13; SPSS Inc., IL, U.S.A.). A p value <0.05 was considered statistically significant.

Results

The relevant baseline characteristics of 85 patients

The age, gender and prevalence of risk factors of coronary artery disease were not different between these two groups of patients (i.e.,historical-control group (n=52) and tacrolimus-treated group (n=29)). In addition, the prevalence of previous stroke, myocardial infarction and PCI were similar between the two groups. There was a trend of more patients with anterior myocardial infarction in the tacrolimus-treated group and more inferior myocardial infarction in the control group (Table 1).

The Killip score upon presentation and the requirement of IABP support were not different between the two groups. However, the occurrence of ventricular tachycardia/ventricular fibrillation at the Emergency Room that required defibrillation was significantly higher in tacrolimus-treated group than the control group (p=0.040). There was a trend of more patients in the prevalence of acute pulmonary edema, mean congestive failure score and advanced congestive heart failure in control group than in tacrolimus-treated group that were observed during hositalization.

The laboratory findings and baseline echocardiographic results

There was no difference in the total cholesterol and low-density lipoprotein levels, white blood count and hemoglobin level between tacrolimus-treated and control groups. However, the high-density lipoprotein level was significantly higher, whereas the creatinine level was significantly lower in tacrolimus-treated group than in the control group. The blood sugar level upon presentation and the peak CK-MB level were not different between the two groups of the patients. However, the hemoglobin A1c level was significantly lower in the tacrolimus-treated group than in the control group. For echocardiography, the baseline left ventricular ejection fraction that was performed within 24 hours after PCI were not differ between the two groups (Table 2).

Door to balloon time, angiographic findings and 30-day mortality

The chest pain onset-to-door time, door-to-balloon time, puncture to reperfusion time and the procedure time were not different between these two patient groups. The incidence of multi-vessel disease, pre-TIMI flow and pre- and post-degree of stenosis of the IRA were similar between the two groups. However, there were trends of more patients in the prevalence of higher final TIM-3 flow and in the ratio of 90-minute ST-resolution of electrocardiogram in tacrolimus-treated group than in control group. Additionally, the myocardial blushing (MB) grade was significantly higher in tacrolimus-treated group than in the control group (2.45 ± 0.51 vs. 2.10 ± 0.72, p=0.034). There was no difference in the recurrent MI, duration of hospitalization and 30 day mortality between the two treatment groups (Table 3).

Discussion

This prospective, single center, pilot study which assessed the safety and initial result of intra-coronary administration of tacrolimus during primary PCI showed significantly higher MB grade to conventional primary PCI. Second, tacrolimus therapy provided a tendency of relatively higher ratio of 90 minute ST-resolution than in that of the historical-control group. Third, as compared with historical-control group tacrolimus treatment offered a tendency of increasing final TIMI-3 flow in the IRA.

One of primary objective in the COAT-STEMI clinical trial is an anticipate of final TIMI-3 flow of 96% in tacrolimus treatment vs. 91.0% in placebo control (please see the information from this COAT-STEMI

Variables	Control (n=52)	Tacrolimus n=29)	p-value
Age (yrs)	59.8 ± 13.5	62.6 ± 11.8	0.349
Male gender	86.5% (45)	89.7% (26)	0.526
Hypertension	65.4% (34)	72.4% (21)	0.252
Diabetes mellitus	36.5% (19)	31.0% (9)	0.618
Current smoking	55.8% (29)	62.1% (18)	0.582
Hypercholesterolemia	46.2% (24)	41.4% (12)	0.909
Previous stroke	9.6% (5)	3.5% (1)	0.256
Previous myocardial infarction	1.9% (1)	6.9% (2)	0.310
Previous PCI	3.9% (2)	3.4% (1)	0.928
Infarct location			
Anterior wall	50.0% (26)	65.5% (19)	0.178
Inferior wall	46.2% (24)	34.5% (10)	0.308
Lateral wall	3.8% (2)	0% (0)	0.285
Killip score upon presentation	1.58 ± 0.68	1.38 ± 0.62	0.194
Killip-1	51.9% (27)	65.5% (19)	0.136
Killip-2	36.5% (19)	27.6% (8)	0.190
Killip-3	9.6% (5)	6.9% (2)	0.676
VT/VF	3.9% (2)	17.2% (5)	0.040
IABP support	7.7% (4)	3.5% (1)	0.447
Pulmonary edema	17.3% (9)	3.5% (1)	0.069
Mean CHF Score*	1.94 ± 0.83	1.72 ± 0.92	0.278
Advance CHF (≥ NYHA Fc 3)†	25.0% (13)	13.8% (4)	0.235

Data were expressed as mean ± SD or % (n).
PCI: Percutaneous Coronary Intervention; VT/VF: Ventricular Tachycardia/ Ventricular Fibrillation; IABP: Intra-aortic Balloon Pump; CHF: Congestive Heart Failure; NYHA: New York Heart
* indicated summation of CHF of functional class I to IV.

Table 1: Baseline clinical characteristics of tacrolimus treatment and control groups.

Variables	Control (n=52)	Tacrolimus (n=29)	p-value
Total cholesterol (mg/dL)	180.9 ± 41.5	182.3 ± 46.5	0.896
LDL (mg/dL)	116.5 ± 35.1	114.3 ± 41.1	0.802
HDL (mg/dL)	41.2 ± 10.0	49.0 ± 18.2	0.017
WBC count (x10^3)	11.3 ± 3.2	10 ± 3.3	0.80
Hemoglobin (gm/dL)	14.1 ± 2.0	14.9 ± 1.6	0.86
Creatinine level (gm/dL)	1.5 ± 1.6	1.1 ± 0.3	0.043
Peak CK-MB (ng/mL)	197.6 ± 121.3	217.1 ± 117.5	0.486
Blood sugar (gm/dL)	167.3 ± 81.5	167.8 ± 83.0	0.979
HbA1c (mg/dl)	7.08 ± 1.96	6.21 ± 0.97	0.035
LVEF (%)	53.9 ± 9.3	51.6 ± 8.7	0. 124

Data were expressed as mean ± SD or %
LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; WBC: White Blood Cell; CK: Creatine Phosphokinase; HbA1c: Hemoglobin A1c; LVEF: Left Ventricular Ejection Fraction.

Table 2: Baseline blood tests and echocardiographic assessment of tacrolimus treatment and control groups.

Variables	Control (n=52)	Tacrolimus (n=29)	p-value
Chest on onset to door	141.9 ± 121.8	138.6 ± 115.5	0.907
Door to puncture time	37.6 ± 27.9	39.7 ± 43.0	0.978
Puncture to reperfusion	17.0 ± 7.8	16.1 ± 6.2	0.548
Procedure time	34.4 ± 16.3	32.3 ± 14.8	0.563
Multiple vessel disease	67.3% (35)	62.1% (18)	0.635
	0.44 ± 0.73	0.35 ± 0.72	0.967
0-1	86.5% (45)	86.2% (25)	
2-3	13.5% (7)	13.8% (4)	
Pre-PCI stenosis (%)	95.6 ± 8.6	96.9 ± 6.6	0.470
	2.90 ± 0.3	2.93 ± 0.26	0.310
0-2	9.6% (5)	3.7% (1)	
3	90.4% (47)	96.6% (28)	
Post-PCI residual stenosis (%)	13.5 ± 6.6	12.7 ± 5.7	0.614
Myocardial blushing grade	2.10 ± 0.72	2.45 ± 0.51	0.034
≥2	82.7% (43)	100% (29)	0.017
3	28.9% (15)	44.8% (13)	0.147
Ratio of 90 min ST-resolution	0.47 ± 0.56	0.66 ± 0.24	0.243
Recurrent MI	0% (0)	0% (0)	1
Duration of hospitalization	7.0 ± 3.6	6.0 ± 2.7	0.176
30-day mortality	1.9% (1)	0% (0)	1

Data were expressed as mean ± SD or % (n). PCI: Percutaneous Coronary Intervention; TIMI: Thrombolysis in Myocardial Infarction; MB: Myocardial Blushing; MI: Myocardial Infarction.

Table 3: Door to balloon time, angiographic s and 30-day clinical outcomes of tacrolimus treatment and control groups.

clinical trial: clinical trials no: ISRCTN38455499). Interestingly, one noteworthy finding in the present study was that the final TIMI-3 flow in the IRA which was as our expected was higher in tacrolimus-treated group than in historical-control group (96.6% vs. 90.4%). Accordingly, our finding supports our anticipation of this clinical trial.

Previous studies have shown that rapid ST-segment resolution in patients undergoing primary PCI was associated with LV contractility recovery and a predictor of favorable clinical outcome [38-40]. In the present study, the second primary end point is an anticipate of 90 minute resolution of ST-segment elevation is better in tacrolimus-treated group than in placebo-control group. In fact that in the present study, we found 90 minute resolution of ST-segment elevation was greater in tacrolimus-treated group than the historical-control group. This finding suggests that the myocardial tissue-level perfusion was better in former group than that in the latter group.

The third primary end point in the COAT-STEMI clinical trial is an anticipate of MB grade, an important indicator of integrity of microvascular circulation, is greater in tacrolimus-treated group than placebo-control group. The most important in the present study was that the MB grade of the IRA was significantly higher in tacrolimus-treated group than in that of historical-control group. Additionally, this study displayed that even the incidence of anterior-wall infarct location was lesser in historical-control group than the tacrolimus-treated group, the prevalence of pulmonary edema and advanced CHF that were observed during hospitalization, on the other hand, were notably higher in the former than in the latter group. These findings may imply that the successfully increased MB grade in the IRA after tacrolimus treatment translated into a restoration of myocardial tissue-level perfusion and preservation of the heart function. Consistently, a strong association between increased MB grade in the IRA and improvement of heart function and favorable prognostic outcome in patients with STEMI undergoing reperfusion therapy have been reported in previous studies [40,41]. Therefore, our finding is consistent with the observation of previous studies and highlight th1at myocardial tissue-level perfusion (i.e., MB grade) is one of the most important factors for predictive of clinical outcome after reperfusion therapy.

The main objective and the one of secondary objectives in the COAT-STEMI clinical trial are the safety issue and 30 day mortality, respectively. The particular importance was that there was no any tacrolimus-related side effect or complication in this pilot study. Additionally, the 30-day mortality in our consecutively enrolled patients was 0%. Accordingly, intra-coronary tacrolimus injection was safe to the patients.

Tacrolimus, also named FK506, is a potent macrolide immunosuppressant acting via the lymphokine signal transduction pathway [42]. Tacrolimus forms the FK506-binding protein (FK-BP) (i.e., immunophilin FKBP12) in cytoplasmic receptor which inactivates calcineurin, a central phosphatase for T cell signaling [42,43]. Interestingly, the final MB grade was better in tacrolimus group than in control group (p=0.034, a weakly statistical significance). We remain uncertain for why about 20 minute later (i.e., from tacrolimus injection to the final procedure time) intra-coronary administration, the favorable effect of tacrolimus therapy was observed in the present study. Perhaps, it could be due to the anti-inflammatory effects of tacrolimus [28-30] through reducing the formation of vascular adhesion molecules, proinflammatory cytokines and the activations of macrophages/leukocytes and platelets in the IRA or due to the fact that it was a small sample size and non-randomized study that distorted the statistically analytical results.

Study Limitation

This study has limitations. First, the objective of this pilot study was to generate initial data using a historical control rather than a double-blinded, randomized, placebo-controlled trial with two parallel arms. Therefore, the potential bias could not be completely ruled out. Second, the sample size of this pilot study was relatively small. Therefore, the truly statistical significance would be distorted in such a smaller sample size.

In conclusion, the results of this pilot study provide evidence for the safety, feasibility and efficacy of this clinical trial design and also yield data to determine the appropriate sample size for future large-scale COAT-STEMI clinical trial in STEMI patients undergoing primary PCI.

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