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PCI

Evaluation of Short- and Long-Term Efficacy of Combined Intracoronary Administration of High-Dose Adenosine and Tirofiban during Primary Percutaneous Coronary Intervention

Yanbing Li, Qiang Li, Feiou Li, Min Zong, Guobin Miao, Xinchun Yang, Zichuan Tong and Jianjun Zhang

Background: To assess the influence of combined intracoronary application of high-dose adenosine and tirofiban in primary percutaneous coronary intervention (PCI) on clinical events and cardiac function.

Methods: Our study evaluated consecutive patients with acute ST-segment elevation myocardial infarction undergoing primary PCI, who were randomly divided into adenosine group (n = 130) and control group (n = 128). Combined with thrombus aspiration and then intracoronary tirofiban, the adenosine group received intracoronary adenosine (2 mg) through the aspiration catheter 2 times. After thrombus aspiration and stenting of the infarct- related artery, the control group received placebo. The primary endpoint of our investigation was major adverse cardiac events (MACE) at the 1-year and 3-year marks. The secondary endpoint comprised left ventricular remodeling (LVR) at 6 months, myocardial blush grade (MBG), thrombolysis in myocardial infarction (TIMI) flow grade and corrected TIMI frame count (CTFC) after PCI.

Results: Our study found that TIMI flow grade post-PCI did not differ significantly between the 2 groups, while CTFC favored the adenosine-treated patients (21.6 ± 6.5 vs. 25.1 ± 7.8, p = 0.001). Although the adenosine group achieved a higher rate of MBG 3 (45.1% vs. 32.0%, p = 0.035) and MBG 2-3 (76.2% vs. 62.3%, p = 0.018) than the control group, the incidences of MACE at 1 year (20.0% vs. 25.0%, p = 0.373) and 3 years (26.9% vs. 32.0%, p = 0.413) were comparable. LVR occurred in 23.1% (27/117) of adenosine-treated patients and in 29.8% (43/114) of the controls (p = 0.296).

Conclusions: Intracoronary administration of high-dose adenosine combined with intracoronary tirofiban and thrombus aspiration may further improve myocardial perfusion after primary PCI.

Key Words: Adenosine • Angioplasty • Myocardial infarction • Remodeling

INTRODUCTION

In the clinical setting of acute ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), no-reflow phenomenon affects more than 20% of patients.[1-3] This "angiographic no-reflow" was associated with reduced myocardial salvage, larger infarct size, poor left ventricular functional recovery and increased risk of short-term mortality.[4-6] It furthermore was an independent predictor of long-term cardiac death and cardiac events in STEMI patients treated with primary PCI.[7,8]

Thus, efforts have been undertaken to reduce the incidence of no-reflow, such as thrombus aspiration[9]

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Heart Center, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China.
Address correspondence and reprint requests to: Dr. Zichuan Tong, Heart Center, Beijing Chaoyang Hospital, Capital Medical University, No. 5, Jing-Yuan Road, Shijingshan District, Beijng 100043, China. Tel: 86-10-51718592; Fax: 86-10-51718055; E-mail: tongzichuan@sina.com

and distal protection device.[10] On the other hand, some agents who administered intravenously or intracoronarily during primary PCI have been demonstrated to be effective. It has been reported that intravenous or intracoronary application of platelet glycoprotein (GP) IIb/IIIa receptor antagonist[11,12] or adenosine,[13,14] could raise the myocardial perfusion level, reduce the incidence of no-reflow, and improve clinical outcomes in patients who underwent primary PCI.

Although a number of studies had evaluated the effects of intravenous or intracoronary application of adenosine in primary PCI, some were limited by their non-controlled design or low sample size, and few had assessed the influence of adenosine on cardiac function and long-term clinical outcomes. In the previous study, it was demonstrated that combined intracoronary administration of high-dose adenosine and tirofiban during primary, and PCI could further reduce the risk of no-reflow.[15] Whether this beneficial effect could translate into advantageous influence on clinical outcomes was worth clarifying. This study with a 3-year follow-up was intended to indentify the influence of combined intracoronary application of high-dose adenosine and tirofiban during primary PCI on clinical events and cardiac function.

PATIENTS AND METHODS

Patients

This was a single-center, open-label, prospective, randomized controlled study. Its eligible participants consisted of consecutive patients over 18 years of age, presenting to the Capital Medical University Beijing Chao-yang Hospital with suspected acute STEMI, as well as candidates for primary PCI who were eligible for participation. Inclusion criteria were: symptoms of chest pain suggestive of myocardial ischemia for at least 30 minutes, less than 12 hours from onset of symptoms to hospital admission, and an electrocardiography (ECG) showing ST-segment elevation of > 0.1 mV in 2 or more leads, or new left bundle branch block. Exclusion criteria were: 1) contraindications for anticoagulant, antiplatelet therapy; 2) left main coronary artery lesion or cardiogenic shock; 3) previous history of coronary artery bypass grafting; 4) any past thrombolytic therapy; 5) second-degree or higher atrioventricular blockage with no cardiac pacing protection; 6) concomitant asthma or chronic obstructive pulmonary disease or history of theophylline, dipyridamole, or glyburide treatment; and 7) life expectancy < 6 months. This study was conducted from January 2007-September 2010. The study protocol was approved by our hospital ethics committee, and all randomized patients gave written informed consent before enrollment.

Randomization and treatment

After an initial coronary angiography was performed, the operator determined if the patient qualified for randomization. The eligible patients were randomized (1:1) to 2 high-dose bolus injections of intracoronary adenosine (2 × 2 mg in 20 mL 0.9% NaCl) or placebo (2 × 20 mL 0.9% NaCl). This occurred after thrombus aspiration and intracoronary injection of tirofiban, and after stenting, by hand distal to the culprit lesion over 1 minute. Sealed sequentially numbered opaque allocation envelopes were used for randomization. Additionally, the allocation schedule was based on computer-generated random numbers (block size 20).

Ultimately, the procedure was performed through the radial (preferred) or femoral artery at the operator's discretion utilizing standard techniques. However, only the culprit lesion was treated. After a guide wire crossing the culprit lesion, manual thrombus aspiration were performed at least 2 times using thrombus aspiration catheter (ZEEK, Zeon Medical, Tokyo, Japan). If the aspiration catheter could not cross the lesion, a predilation could be conducted. Then, through the aspiration catheter, a bolus of 10 μg/kg tirofiban was injected by hand distal to the culprit lesion over 3 minutes, followed by continuous intravenous administration at 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 24 h. Intracoronary nitroglycerin (200 ug) administered through the guiding catheter was recommended after the 2 times bolus of intracoronary adenosine or placebo. Other medications, such as sodium nitroprusside, verapamil, and diltiazem, were not routinely recommended but were applied when necessary.

Before the procedure was conducted, all patients received 300 mg of aspirin and 600 mg of clopidogrel. Unfractionated heparin was administered, with a bolus of 70 IU/Kg given via the arterial sheath, maintaining an activated clotting time of 250 seconds or longer. Aspirin

(75 to 100 mg/day) was prescribed indefinitely and clopidogrel (75 mg/day) for at least 12 months after procedure. Patients were treated with beta blocking agents, statins, and angiotensin-converting enzyme inhibitors or angiotensin II blockers according to the judgment of the patients' physician.

Angiographic and electrocardiographic analysis

Coronary angiograms obtained before and after primary PCI were analyzed by two experienced observers blinded to treatment allocation and clinical data. On the initial angiogram and on the angiogram after stenting, thrombolysis in myocardial infarction (TIMI) flow grade[16] was assessed. In addition, corrected TIMI frame count (CTFC) and myocardial blush grade (MBG) were assessed after stenting, as previously described.[17,18] The 12-lead ECG obtained upon presentation and post-intervention were used to measure ST-segment elevation at 20 ms after the QRS complex. For anterior myocardial infarction, leads I, aVL, and V1-V6 were measured; for non-anterior myocardial infarction, leads II, III, aVF, and V5-V6 were measured. The sum of ST-segment resolution (sum STR) was calculated, and categorized as complete resolution (> 70%), partial resolution (30-70%), and no resolution (< 30%).[19]

Myocardial biomarkers

Serum creatine kinase (CK), myocardial band of CK (CK-MB), and troponin I (Tn-I) were measured in all patients on admission, just before and after primary PCI, and at 8, 16, 24 and 48 hours after the procedure. The maximal value was defined as the peak value.

Echocardiographic study

All subjects underwent two 2-dimensional echocardiographic examinations, at discharge and 6 months after the procedure, with the commercially available ultrasound scanner iE33 (Philips; Andover, MA, USA). LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV ejection fraction (LVEF) were calculated by the modified biplane Simpson's rule algorithm.[20] Left ventricular remodeling (LVR) was defined as a $\geq$ 20% increase in the LVEDV at 6-month follow-up assessed as compared with that at the time of discharge.[21]

Follow-up and endpoints

Clinical follow-up was performed at 30 days, 3 months, 6 months, and then every 6 months for a total of 3 years after the procedure. The primary end point of the study was major adverse cardiac events (MACE), defined as the composite of cardiac death, recurrent infarction, target vessel revascularization (TVR), and heart failure (defined as cardiac function $\geq$ NYHA class II combined with LVEF < 50%) at the 1-year and 3-year marks. The secondary endpoints comprised LVR at 6 months, and TIMI flow grade, CTFC, and MBG after revascularization. Stent thrombosis (ST) was classified as definite, probable, and possible according to the Academic Research Consortium definition. The clinical events committee, whose members were blinded to the assigned groups, reviewed and adjudicated all serious clinical events.

Statistical analysis

According to the medical records, the incidence of no-reflow in the control group was approximately 45%,[1-3,13,14] and adenosine application reduced the incidence of no-reflow by approximately 15%.[13,14] Based on a sample size calculation formula with α set at 0.05, statistical significance was set at a sample size of 120 per group, with a total required sample size of 240. Continuous data are expressed as mean $\pm$ standard deviation (SD) or as median (interquartile range), and dichotomous data are presented as numbers and percentages. All continuous variables were compared using the Student's t-test or, in the case of a non-Gaussian distribution, with a nonparametric test. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test as appropriate. Three-year event curves were generated by the Kaplan-Meier method, and incidence between groups was compared utilizing the log-rank test. Hazard ratios with 95% confidence intervals were calculated by Cox proportional hazards regression model. A 2-sided p value < 0.05 was considered significant for all tests. All analyses were conducted using SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

A total of 392 STEMI patients who received primary PCI were screened, after which 264 patients were enrolled in the present study. Among these patients, 3 in

the adenosine group ceased intravenous tirofiban due to bleeding and were excluded (one case of hematochezia, one of stress ulcer combined with upper gastrointestinal bleeding, and one for bleeding gums). Additionally, 2 patients in the control group stopped administration of tirofiban due to bleeding (one case of stress ulcer combined with upper gastrointestinal bleeding and one for epistaxis), and were excluded. One case in the control group ceased application of tirofiban due to a substantial decrease in platelet count (< 50×10^9/L) and was excluded. Ultimately, data of 130 patients in the adenosine group and 128 patients in the control group were analyzed. The two groups did not differ significantly in basic clinical information, coronary angiogram, or PCI data (Table 1).

Angiographic results

There was no significant difference in the TIMI flow

Table 1. Baseline characteristics

	Adenosine group (n = 130)	Control group (n = 128)	p value
Age (years)	61.5 ± 11.7	60.2 ± 12.5	0.595
Male	102 (78.5)	95 (74.2)	0.465
Heart rate (bpm)	76.5 ± 17.8	75.0 ± 18.2	0.451
Systolic blood pressure (mmHg)	129.3 ± 25.8	131.7 ± 23.8	0.659
Diastolic blood pressure (mmHg)	76.4 ± 14.2	75.1 ± 14.4	0.528
Current smoker	80 (61.5)	69 (53.9)	0.257
History			
Hypertension	55 (42.3)	58 (45.3)	0.707
Diabetes	22 (16.9)	27 (21.1)	0.430
Hyperlipidemia	46 (35.3)	41 (32.0)	0.600
Myocardial infarction	4 (3.0)	3 (2.3)	1.000
PCI	7 (5.4)	5 (3.9)	0.769
Family history	38 (29.2)	30 (23.4)	0.324
Ischemic time (min)	214 ± 147	225 ± 152	0.772
Killip class			0.891
I	97 (74.6)	94 (73.4)	
II	27 (20.8)	29 (22.7)	
III	6 (4.6)	5 (3.9)	
Angiographic			
Infarct-related vessel			0.872
LAD	62 (47.7)	57 (44.5)	
LCX	18 (13.8)	18 (14.1)	
RCA	50 (38.5)	53 (41.4)	
Multivessel disease	75 (57.7)	70 (54.7)	0.707
TIMI flow pre-PCI			0.652
Grade 0, 1	85 (65.4)	81 (63.3)	
Grade 2	19 (14.6)	24 (18.8)	
Grade 3	26 (20.0)	23 (17.9)	
Primary PCI			
Stent diameter (mm)	3.3 ± 0.47	3.3 ± 0.49	0.695
Stent length (mm)	25.1 ± 12.5	24.2 ± 13.6	0.429
Direct stenting	22 (16.9)	26 (20.3)	0.525
Post-stent dilation	102 (78.5)	94 (73.4)	0.383
DES use	126 (96.9)	125 (97.7)	1.000
IABP use	4 (3.1)	4 (3.1)	1.000

Data are presented as mean (SD) or n (%), except where noted.

DES, drug eluting stent; IABP, intra-aortic balloon counterpulsation; LAD, left artery descendent; LCX, circumflex artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

grade after procedure between the adenosine group and the control group, with 123 (94.6%) and 118 (92.2%) patients achieving TIMI grade 3 flow, respectively (p = 0.625). The CTFC of the adenosine group was significantly more favorable than that of the control group (21.6 ± 6.5 frames vs. 25.1 ± 7.8 frames, p = 0.001) (Table 2). MBG evaluation revealed that the rate of MBG 3 [45.1% (55/122) vs. 32.0% (39/122), p = 0.035] and of MBG 2-3 [76.2% (93/122) vs. 62.3% (76/122), p = 0.018] were significantly higher in the adenosine group than that in the control group (Table 2).

ST-segment resolution

The ECG results of 125 patients in the adenosine group and 124 patients in the control group were reviewed for sum STR analysis. The ECGs were recorded at 29 min (20-42 min) in the adenosine group and 32 min (18-45 min) in the control group after PCI. The rates of complete ST-segment resolution were comparable between the two groups [53.6% (67/125) vs. 41.9% (52/124), p = 0.065] (Table 2).

Biomarkers

In the adenosine group, the peak values of CK (1738 ± 772 U/L vs. 1975 ± 897 U/L, p = 0.023), CK-MB (124 ± 51 U/L vs. 141 ± 57 U/L, p = 0.009) and Tn-I (75 ± 26 ng/ml vs. 84 ± 29 ng/ml, p = 0.011) were all significantly lower than those in the control group.

Table 2. Myocardial reperfusion after primary percutaneous coronary intervention (n, %)

	Adenosine group	Control group	p value
TIMI flow grade	n = 130	n = 128	
0 or 1	1 (0.8)	2 (1.5)	0.552
2	6 (4.6)	8 (6.3)	0.562
3	123 (94.6)	118 (92.2)	0.432
CTFC	n = 119	n = 116	
Frames, x ± s	21.6 ± 6.5	25.1 ± 7.8	0.001
MBG	n = 122	n = 122	
0	7 (5.7)	14 (11.5)	0.110
1	22 (18.0)	32 (26.2)	0.123
2	38 (31.2)	37 (30.3)	0.890
3	55 (45.1)	39 (32.0)	0.035
Sum STR	n = 125	n = 124	
< 30%	20 (16.0)	29 (23.4)	0.143
30%-70%	38 (30.4)	43 (34.7)	0.471
> 70%	67 (53.6)	52 (41.9)	0.065

CTFC, corrected TIMI frame count; MBG, myocardial blush grade; STR, ST-segment resolution; TIMI, thrombolysis in myocardial infarction.

Echocardiographic results

Data of echocardiographic examinations achieved at discharge and at 6 months after the procedure of 117 adenosine patients and 114 controls had been analyzed. The adenosine group and the control group showed similar LVEDV (121 ± 31 mL vs. 122 ± 32 mL, respectively; p = 0.681), LVESV (70 ± 31 mL vs. 74 ± 29 mL, respectively; p = 0.277), and LVEF (42 ± 14% vs. 40 ± 12%, respectively; p = 0.519) at discharge and at 6 months (LVEDV 125 ± 38 mL vs. 130 ± 42 mL, respectively, p = 0.417; LVESV 64 ± 29 mL vs. 69 ± 30 mL, respectively, p = 0.374; LVEF 49 ± 15% vs. 47 ± 12%, respectively, p = 0.319). There were 27 patients in the adenosine group and 34 patients in the control group exhibiting LVR (p = 0.296).

Clinical outcomes

All patients in both groups fulfilled their follow-up at 30 days and 1-year. However, two cases in the adenosine group and one case in the control group were lost to follow-up at 3-year. The two groups did not differ significantly in the incidence of MACE or heart failure at 30 days (Table 4). Additionally, the two groups received similar medical treatments (Table 3), and showed comparable incidence rates of cardiac death, re-infarction, TVR, heart failure, or MACE at 1-year and 3-year follow-

Table 3. Medication status

	Adenosine group	Control group	p value
At 1 year	n = 130	n = 128	
Aspirin	128 (98.5)	126 (98.4)	1.000
Clopidogrel	129 (99.2)	128 (100)	1.000
Betablocking agents	96 (73.8)	91 (71.1)	0.677
ACEI or ARB	95 (73.1)	98 (76.6)	0.567
Statin	122 (93.8)	122 (95.3)	0.785
At 3 years	n = 128	n = 127	
Aspirin	122 (95.3)	120 (94.5)	0.785
Clopidogrel	20 (15.6)	23 (18.1)	0.620
Betablocking agents	96 (75.0)	92 (72.4)	0.671
ACEI or ARB	85 (66.4)	90 (70.9)	0.500
Statin	118 (92.2)	120 (94.5)	0.617

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II blockers.

up (Table 4, Figure 1). Cumulative ST event rates up to 3 years after the procedure were similar between the 2 groups (Table 4). The 3-year cumulative incidence of heart failure was 18.5% and 23.4% in the adenosine group and the control group (p = 0.31; HR 0.76, 95%CI 0.44-1.30), respectively, and the rate of MACE was 26.9% and 32.0% in the 2 groups (p = 0.35; HR 0.81, 95%CI 0.51-1.27) (Figure 1).

Table 4. Clinical outcomes (n, %)

	Adenosine group	Control group	p value
At 30 days	n = 130	n = 128	
Death	1 (0.8)	2 (1.6)	1.000
Cardiac death	1 (0.8)	1 (0.8)	1.000
Recurrent infarction	1 (0.8)	1 (0.8)	1.000
TVR	0	1 (0.8)	1.000
Heart failure	14 (10.8)	20 (15.6)	0.274
MACE	16 (12.3)	22 (17.2)	0.295
At 1 year	n = 130	n = 128	
Death	4 (3.1)	4 (3.1)	1.000
Cardiac death	3 (2.3)	3 (2.3)	1.000
Recurrent infarction	1 (0.8)	2 (1.6)	1.000
TVR	3 (2.3)	4 (3.1)	1.000
Heart failure	19 (14.6)	26 (21.1)	0.253
MACE	26 (20.0)	32 (25.0)	0.373
At 3 years	n = 128	n = 127	
Death	6 (4.7)	7 (5.5)	0.785
Cardiac death	4 (3.1)	5 (3.9)	0.749
Recurrent infarction	5 (3.9)	5 (3.9)	1.000
TVR	7 (5.5)	9 (7.1)	0.617
Heart failure	24 (18.5)	30 (23.4)	0.360
MACE	35 (26.9)	41 (32.0)	0.413
Stent thrombosis	4 (3.1)	4 (3.1)	1.000
Definite	1 (0.8)	2 (1.6)	0.622
Probable	2 (1.6)	1 (0.8)	1.000
Possible	1 (0.8)	1 (0.8)	1.000

MACE, major adverse cardiac events; TVR, target vessel revascularization.

DISCUSSION

The present study suggests that, for STEMI patients undergoing primary PCI, on the basis of thrombus aspiration and intracoronary tirofiban infusion, intracoronary bolus of high-dose adenosine (2 mg, 2 times) through aspiration catheter can further improve myocardial perfusion and reduce the incidence of no-reflow, with a trend of promoting ST-segment resolution. However this benefit would not likely improve clinical cardiovascular events and cardiac function.

Many methods and criteria have been applied to evaluate and diagnose no-reflow in PCI. Due to the difference in subjects, methods of evaluation, and diagnostic criteria among different studies, the incidence of no-reflow reported covered a wide range, from 5-50%.[22] As coronary angiographic criteria, no-reflow is defined as TIMI grade < 3 or TIMI grade 3 but MBG grade 0-1. When using ST-segment resolution for evaluation of myocardial perfusion, only about 35% of patients could achieve sufficient myocardial tissue perfusion (defined as STR > 70%) after primary PCI.[22] In the present study, more patients in the adenosine group achieved MBG 2-3 after primary revascularization, namely reducing the

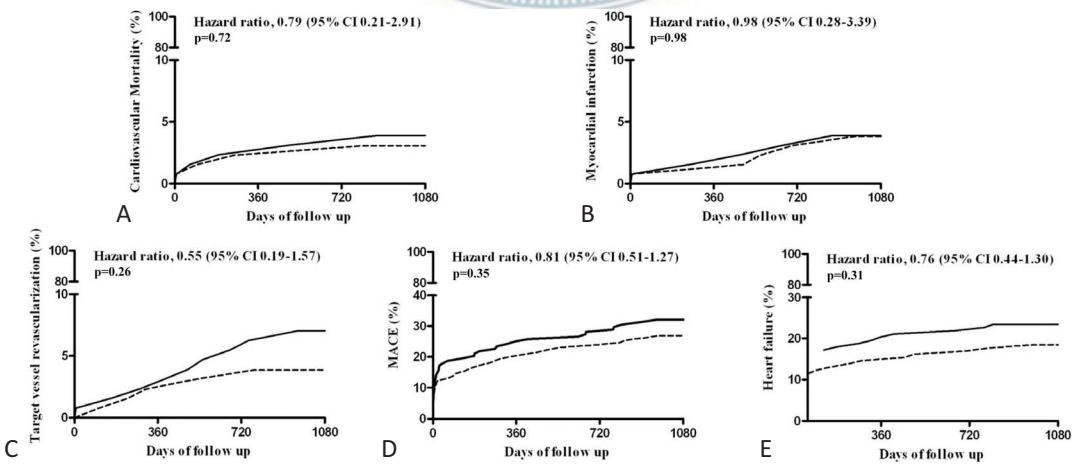

Figure 1. *Clinical outcomes with three-year follow-up.*

incidence of angiographic no-reflow.

Many factors contribute to no-reflow, including distal embolization, coronary spasm, ischemia-related and reperfusion-related injury. Coronary microvascular dysfunction and ischemia-reperfusion injury are important mechanisms. A variety of medications [e.g., verapamil, diltiazem, sodium nitroprusside, adenosine, and glycoprotein IIb/IIIa inhibitors (GPI)] and measures (e.g., thrombus aspiration and distal protection devices) targeting different pathological aspects of no-reflow have been explored to reduce the risk of no-reflow. The efficacy of thrombus aspiration[9,23] and application of GPI[11,12] in reducing no-reflow during primary PCI has been demonstrated. Medication bolus injected through the thrombus aspiration catheter into the infarct-related coronary artery is a simple and effective method. During primary PCI, combined with thrombus aspiration intracoronary administration of GPI, adenosine, and other medications through the aspiration catheter may be an effective means to further improve myocardial perfusion.

The mechanisms of action of adenosine are multifaceted and not yet entirely clear. In circumstances involving ischemia, myocardial cells produce endogenous adenosine. Experimental studies have shown that adenosine has a strong effect on vasodilation, and the capacity to inhibit platelet aggregation, inflammatory cell activation, oxygen free radical production, and intracellular calcium influx. In this manner, adenosine can reduce the severity of reperfusion injury and improve myocardial perfusion.[24,25] Acute Myocardial Infarction STudy of ADenosine (AMISTAD)-I trial[26] and the AMISTAD-II[27] trial have shown that intravenous use of high doses of adenosine (70 μg/kg/min) could reduce infarction area. Intracoronary use of adenosine can offer a higher local concentration and less side effects. Intracoronary administration of high doses of adenosine during primary PCI have been shown to be safe and improve myocardial perfusion, reduce the incidence of no-reflow, promote ST-segment resolution, and narrow the infarction size.[13,14,28,29] However, these studies included a limited number of samples, and some of them were not randomized controlled trials. In the subsequent two randomized controlled studies, the efficacy of intracoronary application of adenosine in primary PCI was not confirmed.[30,31] Using cardiac magnetic resonance imaging (MRI), Desmet et al.[30] found that intracoronary injection of adenosine (4 mg) during primary PCI could not improve MBG after and salvage more myocardium. In another study recruiting 448 STEMI patients, intracoronary bolus of adenosine (120 μg, twice) in primary PCI also failed to improve myocardial perfusion.[31]

Unfortunately, improvement of myocardial perfusion failed to benefit clinical outcomes at 1-year and 3-year, and cardiac function and LVR at 6 months in this study. To date, studies on intravenous or intracoronary use of adenosine during primary PCI had not demonstrated any advantageous influence on long-term clinical events. The potential causation of such lack of correlation may include the following: 1) the sample size may not being large enough; 2) even though intravenous and intracoronary administration of adenosine can reduce myocardial necrosis, the extent may not being enough to lead to a decrease of clinical events; 3) the use of β-blockers, ACEI or ARB and statins improving ventricular remodeling after myocardial infarction, reducing the incidence of clinical events, and thus desalinating the possible clinical benefits of adenosine.

Although it remains controversial to apply a prophylactic application of adenosine to all STEMI patients undergoing primary PCI, prophylactic use of adenosine targeting patients at high risk of no-reflow or therapeutic intracoronary administration of adenosine in patients with poor myocardial perfusion after intervention is a worthwhile undertaking.[29] The efficacy of intracoronary administration of adenosine targeting these patients awaits further exploration.

CONCLUSIONS

In conclusion, this study confirmed that intracoronary administration of high-dose adenosine could further improve myocardial perfusion during primary PCI. However, whether this effect could benefit clinical outcomes and cardiac function needs further evaluation

CONFLICT OF INTEREST

There is no conflict of interest in this manuscript.

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