# Effect of Intravenous Administration of Liposomal Prostaglandin E1 on Microcirculation in Patients with ST Elevation Myocardial Infarction Undergoing Primary Percutaneous Intervention

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## Abstract

**Background:** Several studies have demonstrated that primary percutaneous coronary intervention (PCI) can result in reperfusion injury. This study aims to investigate the effectiveness of liposomal prostaglandin E1 (Lipo-PGE1, Alprostadil, Beijing Tide Pharmaceutical Co., Ltd.) for enhancing microcirculation in reperfusion injury. In addition, this study determined the optimal administration method for acute ST elevation myocardial infarction (STEMI) patients undergoing primary PCI.

**Methods:** Totally, 68 patients with STEMI were randomly assigned to two groups: intravenous administration of Lipo-PGE1 (Group A), and no Lipo-PGE1 administration (Group B). The corrected thrombolysis in myocardial infarction (TIMI) frame count (cTFC) and myocardial blush grade (MBG) were calculated. Patients were followed up for 6 months. Major adverse cardiac events (MACE) were also measured.

**Results:** There was no significant difference in the baseline characteristics between the two groups. The cTFC parameter in Group A was significantly lower than Group B ($18.06 \pm 2.06$ vs. $25.31 \pm 2.59$, $P < 0.01$). The ratio of final MBG grade-3 was significantly higher ($P < 0.05$) in Group A (87.9%) relative to Group B (65.7%). There was no significant difference between the two groups in final TIMI-3 flow and no-reflow. Patients were followed up for 6 months, and the occurrence of MACE in Group A was significantly lower than that in Group B (6.1% vs. 25.9% respectively, $P < 0.05$).

**Conclusions:** Myocardial microcirculation of reperfusion injury in patients with STEMI, after primary PCI, can be improved by administering Lipo-PGE1.

**Key words:** Intravenous Administration; Liposomal Prostaglandin E1; Primary Percutaneous Coronary Intervention; ST Elevation Myocardial Infarction

## INTRODUCTION

Significant improvements in the survival of patients with ST-segment elevation myocardial infarction (STEMI) have been achieved with primary percutaneous coronary intervention (PCI),[1] which produces immediate recanalization and thus reduces infarction size and mortality rate. However, experimental and clinical studies have demonstrated that myocardial impairment, known as reperfusion injury, may occur as a result of reperfusion. Recent reports have determined that the reperfusion injury is improved by administration of verapamil,[2] nicorandil,[3-5] adenosine,[6,7] nitroprusside,[8] anisodamine,[9] or prostaglandin E1 (PGE1)[10,11]. PGE1 reduces free radical production in stimulated human neutrophils and may attenuate reperfusion injury. Researchers have previously shown that PGE1 can improve coronary blood flow,[12] and decrease infarct size[13] in animals. The use of PGE1 in therapy for the myocardial microcirculation in reperfusion injury has not been investigated. Therefore, the present study was designed to assess the effectiveness of treating patients with liposomal PGE1 for enhancing myocardial microcirculation in reperfusion injury and to determine the optimal administration method for STEMI patients undergoing reperfusion therapy.

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## Methods

### Study design

Totally, 68 consecutive STEMI patients, treated with primary PCI, were prospectively enrolled from a total of 116 primary PCIs performed at our institution between January 2013 and October 2014. The patients had grade 0 or 1 thrombolysis in myocardial infarction (TIMI) during initial coronary angioplasty within 12 h of the onset of symptoms. They were randomly divided into two groups according to a random number table: (1) Intravenous administration of liposomal PGE1 (Lipo-PGE1, Alprostadil, Beijing Tide Pharmaceutical Co., Ltd.) (Group A), and (2) a control group no Lipo-PGE1 administration (Group B). Lipo-PGE1 (20 µg) was intravenously injected after coronary angiography immediately in Group A patients (33 patients, 66.2 ± 8.1 years, 18 male). Saline was used in the Group B (35 patients, 65.4 ± 7.9 years, 19 male).

All patients were admitted to our coronary care unit with chest pain, persistent ST-segment elevation, cardiac troponin I (TnI) elevation, and/or regional wall motion abnormalities.[14] Exclusion criteria for all patients were: Age >75 years, previous ECG abnormalities that could prevent the recognition of ST-segment shift, recent or chronic infective or inflammatory diseases, malignancy, surgery or trauma in the previous month, or a history of coronary artery bypass grafting, previous MI, and cardiogenic shock. Patients undergoing rescue PCI were also excluded.

All patients received aspirin (300 mg, i.v.) and clopidogrel (600 or 300 mg if already on clopidogrel) plus standard heparin to maintain an activated clotting time of >300 s. The use of glycoprotein IIb/IIIa inhibitors, thrombus aspiration, and drug-eluting stents was left to the decision of the interventionist. Local Ethics Committee approved the study, and all patients signed an informed consent form. All procedures were followed in accordance with the ethical standards of the responsible committees on human experimentation and with *the Helsinki declaration*.

The primary composite endpoint consisted of major adverse cardiac events (MACE), including re-infarction, revascularization, heart failure and death. The secondary endpoint was the combined outcome of corrected TIMI frame count (cTFC) and myocardial blush grade (MBG).

### Corrected thrombolysis in myocardial infarction frame count and myocardial blush grade

Diagnostic coronary angiography and PCI were performed by the insertion of a 6-French (Fr) arterial sheath via the radial artery using the Seldinger method after local anesthesia. Angiography CDs of the patients were reviewed by two interventional cardiologists who were blinded to all data other than the coronary angiograms. TIMI frame count (TFC) was measured by a digital system in the catheterization laboratory. TFC is the number of cine-frames required for contrast to reach a standardized distal coronary landmark in the culprit vessel and was determined by a previously suggested method.[15] The first frame was selected when the column of the contrast extended across >70% of the arterial lumen with antegrade flow.[16] The reported number was based on a cine filming rate of 25 frames per second. The last frame is a distal landmark to which the contrast enters. Distal landmark in the right coronary artery (RCA) is the first branch of the posterolateral extension of the RCA after the origin of the posterior descending artery. In the circumflex artery, it is the most distal branch of the obtuse marginal branch, which included the culprit lesion. In the left anterior descending (LAD) artery, it is a distal bifurcation that is typically placed at the apex of the heart. cTFC means that the TFC for LAD must be corrected by dividing it into 1.7 due to the longer length of the LAD. All participants with a cTFC > 27 for the particular vessel were accepted as having slow reflow.[15] TFC in the LAD and LCX were assessed in a right anterior oblique projection with caudal angulation and RCA in left anterior oblique projection with cranial angulation.[15]

Myocardial blush grade was performed on cine film at 25 frames/s recorded in a digital coronary imaging catheterization laboratory. In each patient, the best projection was selected to assess the myocardial region perfused by the IRA. Angiographic runs had to be long enough to allow some filling of the venous coronary system, and backflow of the contrast agent into the right atrium had to be present to be certain of adequate contrast filling of the epicardial coronary artery. All angiograms were performed with 6- Fr guiding catheters in a standardized fashion and were given immediately after PCI. This procedure allowed for quantitative coronary artery analysis. MBGs were defined according to the van't Hof *et al*. study.[17]

### Clinical follow-up

Patients were followed up for 6 months. MACE, including re-infarction, revascularization, heart failure and death, were obtained from telephonic interviews with patients or next of kin (where applicable).

### Statistical analysis

Quantitative variables were presented as mean ± standard deviation and categorical variables as percentage. Student's *t*-test or one-way analysis of variance was used for comparison of quantitative data between different groups. Chi-square test was used for comparing qualitative data. A two-sided $P < 0.05$ was considered as statistically significant. The SPSS 13.0 statistical software package (SPSS Inc., Chicago, IL, USA) was used for all calculations.

## Results

### Patient characteristics

Altogether, 68 patients participated in the trial: 33 in Group A and 35 in Group B. Table 1 presents baseline characteristics of the studied population. There were no significant differences between the two groups regarding baseline characteristics.

### Angiographic results

Table 2 compares the PCI characteristics of the patients. The mean door-to-balloon time in Group A and Group B was

45.16 ± 6.73 and 49.43 ± 2.66 min respectively (*P* > 0.05). The mean onset-to-balloon time in Group A and Group B was 5.51 ± 2.86 and 5.81 ± 3.72 h respectively (*P* > 0.05). There were no significant differences between the two groups regarding clinical characteristics.

There were no statistically significant differences in cTFC and TIMI flow between the two groups before primary PCI. However, considerable improvements of coronary flow in the two groups were observed immediately after the operation. Although there was less "no-reflow" observed initially, and more final TIMI-3 flow was elevated toward the end of the measurement period, after PCI, in Group A relative to Group B. However, there was no significant difference between the two groups (*P* > 0.05). In addition, final cTFC in Group A decreased significantly compared to Group B (18.06 ± 2.06 vs. 25.31 ± 2.59, *P* < 0.01). The ratio of final MBG grade-3 in Group A was 87.9%, and 65.7% in Group B (*P* < 0.05) [Table 2].

### Follow-up results in 6 months

Patients were followed up for 6 months, and the occurrence of MACE in Group A was significantly lower than that in Group B (6.1% vs. 25.9%, *P* < 0.05). One patient (3.0%) in Group A and 3 patients (8.6%) in Group B underwent target lesion revascularization. Heart failure occurred in 1 patient (3.0%) in Group A and in 6 patients (17.1%) in Group B as shown in Table 3.

## DISCUSSION

The major finding of this study was that intravenous administration of 20 μg of Lipo-PGE1 prior to PCI, could improve myocardial microcirculation in reperfusion injury without causing any adverse effect. It has recently been shown that the no-reflow phenomenon occurs in approximately one-third of patients treated successfully with coronary angioplasty for AMI.[18,19] The mechanism of the no-reflow phenomenon is still unclear. Microvascular damage and other mechanisms following reperfusion therapy for AMI are hypothesized to limit the completeness of tissue perfusion, despite the reopening of the epicardial vessel.[20] In the microvascular injury hypothesis, despite recanalization of the occluded artery, reperfusion at the level of the microcirculation may remain impaired because of microvascular reperfusion injury. Due to the combined effect of altered mitochondrial metabolism, xanthine oxydase, white blood cells, and complement, more reactive oxygen species are generated, which accelerates microvascular injury.[21] Endothelin and other vasoconstrictors are secreted as a result and also play a role in the microvascular reaction and vasospasm.[22] There are several treatments for no-reflow, depending on the mechanism of this phenomenon. In the atheroembolic theory, platelets play the most important role, so the treatment includes antiplatelet drugs such as a glycoprotein IIb/IIIa receptor blocker.[23,24] In case of vasoconstriction and microvascular injury, vasodilators such as adenosine also can be used.

### Table 1: Clinical characteristics between Group A and Group B

| Variables | Group A (*n* = 33) | Group B (*n* = 35) | *P* |
|---|---|---|---|
| Age (years) | 66.2 ± 8.1 | 65.4 ± 7.9 | 0.167 |
| Male gender, *n* (%) | 18 (54.5) | 19 (54.3) | 0.982 |
| Diabetes, *n* (%) | 11 (33.3) | 13 (37.1) | 0.742 |
| Hypertension, *n* (%) | 25 (75.8) | 28 (80.0) | 0.673 |
| Smoking, *n* (%) | 17 (51.5) | 16 (45.7) | 0.632 |
| BMI (kg/m²) | 24.8 ± 3.6 | 23.9 ± 3.3 | 0.934 |
| LVEF (%) | 52.6 ± 8.8 | 53.1 ± 8.4 | 0.847 |

There was no significant difference in any comparison between two groups or subgroups (all *P* > 0.05). Continuous variables are expressed as mean ± SD and categorical variables as *n* (%). BMI: Body mass index; LVEf: Left Ventricular ejection fraction; SD: Standard deviation.

### Table 2: PCI characteristics between Group A and Group B

| Variables | Group A (*n* = 33) | Group B (*n* = 35) | *P* |
|---|---|---|---|
| Door-to-balloon time (min) | 45.16 ± 6.73 | 49.43 ± 2.66 | 0.649 |
| Onset-to-balloon time (h) | 5.51 ± 2.86 | 5.81 ± 3.72 | 0.682 |
| Culprit vessel, *n* (%) | | | |
| LAD | 15 (45.4) | 18 (51.4) | 0.622 |
| LCX | 9 (27.3) | 8 (22.9) | 0.674 |
| RCA | 9 (27.3) | 9 (25.7) | 0.884 |
| GP IIb/IIIa inhibitors, *n* (%) | 6 (18.2) | 11 (31.4) | 0.207 |
| Thrombus aspiration, *n* (%) | 10 (30.3) | 14 (40.0) | 0.403 |
| Final TIMI-3 flow, *n* (%) | 30 (90.9) | 26 (74.3) | 0.072 |
| Final cTFC (frames) | 18.06 ± 2.06 | 25.31 ± 2.59 | <0.001† |
| Final MBG-3, *n* (%) | 29 (87.9) | 23 (65.7) | 0.031* |
| No reflow, *n* (%) | 1 (3.03) | 6 (17.1) | 0.129 |

*P* < 0.05; †*P* < 0.01. Continuous variables are expressed as mean ± SD and categorical variables as *n* (%). LAD: Left anterior descending; LCX: Left circumflex; RCA: Right coronary artery; GP: Glycoprotein; TIMI: Thrombolysis in myocardial infarction; cTFC: Corrected TIMI frame count; MBg: Myocardial blush grade; SD: Standard deviation; PCI: Percutaneous coronary intervention.

### Table 3: MACE during 6-months follow-up

| Variables | Group A (*n* = 33) | Group B (*n* = 35) | *P* |
|---|---|---|---|
| MACE, *n* (%) | 2 (6.1) | 9 (25.7) | 0.028* |
| Death, *n* (%) | 0 (0) | 0 (0) | 1.000 |
| Re-infarction, *n* (%) | 0 (0) | 0 (0) | 1.000 |
| Revascularization, *n* (%) | 1 (3.0) | 3 (8.6) | 0.649 |
| Heart failure, *n* (%) | 1 (3.0) | 6 (17.1) | 0.129 |

*P* < 0.05. Heart failure: Left ventricular ejection fraction <40%, signs and symptoms of heart failure. MACE: Major adverse cardiac events.

In the present study, we found that intravenous administration of Lipo-PGE1 could significantly decrease cTFC and increase MBG, after PCI, in STEMI patients. Kawamura *et al.* reported that PGE1 reduced myocardial reperfusion injury by inhibiting proinflammatory cytokine production of interleukin-6 (IL-6) and IL-8 during cardiac surgery.[25] Another experimental porcine model, of myocardial infarction reperfusion no-reflow, reported that

Lipo-PGE1 is cardioprotective and decreases the no-reflow area while attenuating the inflammatory response.[10] This, in some ways, may explain the improvement of coronary microcirculation (cTFC and MBG) in our study. During 6-month follow-up, we found that patients receiving intravenous Lipo-PGE1 had less MACE, which was consistent with previously published studies.

## Study limitations

This study was limited by the small population of the STEMI patient following PCI and was a pilot study aimed at examining the effects of Lipo-PGE1 for myocardial microcirculation reperfusion injury for intravenous administration. Due to the absence of similar studies to date, further research is required to establish the effectiveness of Lipo-PGE1, with a larger sample size. This study was a single center study of a small sample number. A large-scale, prospective, randomized study of a Lipo-PGE1 therapy group, intravenous administration or intracoronary administration, should be performed.

In conclusion, myocardial microcirculation reperfusion injury in patients with STEMI, after primary PCI, can be improved by intravenous administration of Lipo-PGE1. Although the number of patients included in the study was relatively small, our clinical observations suggest that Lipo-PGE1 has beneficial clinical outcomes. Lipo-PGE1 deserves further evaluation in the management of STEMI patients undergoing primary PCI.

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