Administration of intracoronary adenosine before stenting for the prevention of no-reflow in patients with ST-elevation myocardial infarction

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ABSTRACT

Objectives: No-reflow phenomenon during the primary percutaneous intervention (PCI) for ST-elevation myocardial infarction (STEMI) is accompanied by a poor clinical outcome and mortality. We aimed to determine the effect of intracoronary adenosine in preventing the no-reflow phenomenon, as detected by three different methods, in patients who underwent primary PCI. Design. In this single-blinded randomized controlled trial, patients with acute STEMI who presented to our center and underwent primary PCI were randomized to the intervention group who received intracoronary adenosine before stenting or the control group who received the standard treatment. No-reflow phenomenon was detected using thrombolysis in myocardial infarction (TIMI) flow grade, TIMI frame count, and myocardial blush grade (MBG). The incidence of the no-reflow phenomenon was then compared between the intervention and control groups. Results. The adenosine group consisted of 110 patients (age = 57 ± 11 years; 92 (84%) male) while 118 patients were in the control group (age = 59 ± 12 years; 89 (75%) male). There was no difference between the study groups in baseline characteristics. The frequency of no-reflow phenomenon was lower in the adenosine group as assessed by TIMI flow grade (15 (14%) vs. 41 (35%)), MBG (23 (21%) vs. 63 (53%)) and TIMI frame count (16 (14%) vs. 50 (42%)) (p < .001 for all). This effect remained significant after adjustment for confounding variables. Conclusion. Intracoronary adenosine could effectively prevent the no-reflow phenomenon in STEMI patients who underwent primary PCI.

Introduction

Primary percutaneous coronary intervention (PCI) has already become the treatment of choice for patients ST-segment elevation myocardial infarction (STEMI) in early hours following the event [1]. However, the use of primary PCI does not necessarily lead to successful coronary revascularization and myocardial reperfusion. Acute reduction in the coronary flow (thrombolysis in myocardial infarction [TIMI] flow grade < 3, Myocardial blush grade [MBG] < 3, or) known as the no-reflow phenomenon, has an incidence of 5-50 percent in STEMI patients who underwent primary PCI [2,3],. Because the no-reflow phenomenon is accompanied by a poor clinical outcome and mortality, utilizing effective preventive measures is of great importance [4].

No-reflow phenomenon has multidimensional pathophysiology, and several factors play a role in the development of no-reflow phenomenon [5,6]. Therefore, various measures have been used for the prevention of no-reflow phenomenon during primary PCI, and many drugs have been administered in this regard, from preprocedural medication to intracoronary agents [7]. Adenosine, an endogenous purine nucleoside, has been used in clinical studies in combination with other agents to prevent no-reflow phenomenon [8,9]. Although the exact mechanism of adenosine is not well-understood, it seems that it acts via inhibition of neutrophil activation and prevention of endothelial damage [10,11]. The study that used intravenous adenosine did not show favorable results, while the intracoronary administration of adenosine had promising outcomes [9,12]. Previous studies had different results due to different methods, the dosage of administered adenosine, and detection methods of no-reflow.

The aim of this study was to determine the effect of intracoronary adenosine in preventing the no-reflow phenomenon, as detected by three different methods, in STEMI patients who underwent primary PCI.

Methods

In this randomized controlled trial, patients with acute STEMI who presented to our center and underwent primary PCI...
PCI were enrolled. The inclusion criteria were the diagnosis of STEMI at the emergency department, having full criteria for primary PCI, TIMI flow grade = 0–1 in the coronary angiography, and giving consent to take part in our study. The exclusion criteria were a cardiogenic shock, complete AV block, severe renal failure (serum creatinine > 3 mg/dl), need for emergent coronary bypass graft surgery, and previous history of coronary revascularization. The study protocol was approved by the institutional board of research and Tehran University of Medical Sciences committee of medical ethics (IR.TUMS.IKHC.REC.1397.349). Also, we registered the protocol at the Iranian Clinical Trial Registry (IRCT20120516009768N6).

STEMI was diagnosed based on the pattern of the electrocardiogram. A clinical history was obtained from the patients, including the history of diabetes mellitus, dyslipidemia, hypertension, and smoking. Also, the baseline values for serum creatinine were recorded for every patient. The patients were considered as diabetic if they used antilglycemic agents or were told by their physician that they have diabetes mellitus. Hypertension was defined as having a systolic blood pressure (BP) ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or use of any antihypertensive medications [13]. Dyslipidemia was defined as being treated for hypercholesterolemia or hypertriglyceridemia or a self-reported history of dyslipidemia. The patients were initially treated by loading doses of clopidogrel 600 mg, and Aspirin 325 mg orally, and routine care for STEMI patients was performed. Glomerular filtration rate was calculated for every patient based on the serum creatinine levels before the procedure using the Modification of Diet in Renal Disease Study equation [14].

Before transfer to the catheterization laboratory, the patients were randomized to the intervention group or control group using an internet-based software that did simple randomization. The randomization was performed using a software generating random numbers. All patients were blinded to the treatment group. The intervention group received a single dose of intracoronary adenosine (Adenorytm®, Vianex, Greece). The dosage included 200 mcg bolus for right side coronary arteries and 400 mcg bolus for the left side coronary arteries through the guiding catheter before stenting. The control group received routine care only.

The coronary angiography was then performed via femoral access. The angiograms were performed using 6 F guiding catheters at the cinefiling speed of 30 frames per second. Primary PCI was performed under the standard protocols by an experienced interventionist [15]. After wiring of the target vessel and resuming of the blood flow in the coronary artery, stenting was performed in all patients. Adenosine was infused just before stenting in the intervention group. All patients received intravenous heparin during the procedures. Using a thrombosuction catheter, administration of glycoprotein IIb/IIIa and balloon pre/post-dilation were at the discerning of the interventionist.

TIMI flow grade, TIMI frame count, and myocardial blush grade (MBG) were utilized to detect the coronary flow and no-reflow phenomenon. TIMI flow grade was based on the degree of flow into the epicardial artery as follows: TIMI grade 0, a complete absence of flow after the obstruction; Grade 1: some flows distal to the obstruction without complete arterial visualization; Grade 2: delayed visualization of the artery; and grade 3: full, prompt visualization of the artery [16]. For the TIMI frame count, the number of cine-frames needed for contrast material to reach distal landmarks was counted based on the standard method [17]. Normal TIMI frame count (TFC) for the left anterior descending artery (LAD) was set below 36 ± 3 (20 ± 3 for corrected TFC), 22 ± 4 for the left circumflex artery, and 20 ± 3 for right coronary artery. MBG was calculated using the method described previously by van’t Hof et al. [18]. MBG ≤ 2 was considered as no-reflow. TIMI flow grade, TIMI frame count, and MBG were evaluated by an experienced cardiologist who was blinded to the study protocol. After the completion of the procedure, the patients were transferred to the post-catheterization department for monitoring and usual care.

The baseline study variables and procedural variables, particularly the incidence of the no-reflow phenomenon, were finally compared between the study groups. The statistician who performed the data analysis was unaware of the study groups.

**Statistical analysis**

Continuous variables were compared between the study groups using the student’s t-test, while categorical variables were compared by the Chi-square test. In order to remove the effect of confounding variables on the no-reflow phenomenon, a multivariate logistic regression analysis was performed for every no-reflow variable, and the results were reported as odds ratios with a 95% confidence interval. Variables with simultaneous effect on the study groups and the outcome and had a p-value < .1 in the univariate analysis were considered as potential confounders. A two-sided probability value (p-value) < .05 was considered as significant. The statistical analysis was performed using SPSS version 21.0 (IBM, Armonk, NY, USA).

**Results**

In this study, 110 patients were recruited in the adenosine group while 118 patients were in the control group. Baseline serum creatinine was not different between the groups (p = .557). There was no difference between the study groups in baseline characteristics, as summarized in Table 1.

Based on the results of the coronary angiography, there was no difference regarding the stenotic vessel. LAD was the most involved coronary artery in both groups. Balloon post-dilation was performed more frequent in the control group (p = .023). On the other hand, glycoprotein IIb/IIIa inhibitor was more used in the adenosine group (p = .025). The incidence of the no-reflow phenomenon was lower in the adenosine group as assessed by TIMI flow grade, MBG, and TIMI frame count (p < .001 for all) (Table 2).
vasodilator effect, also has anti-inflammatory and antiplatelet effects [21]. Therefore, it has appeared as an effective drug in the prevention of no-reflow phenomenon.

An early experimental study that used intracoronary adenosine showed that it could reduce infarct size and improve myocardial wall function [10]. Later studies on humans confirmed this effect and showed that adenosine acts by reducing neutrophil-mediated injury to coronary endothelium [11]. Later, adenosine was used successfully as a preventive measure for the no-reflow phenomenon [22]. Since then, various studies have investigated the usefulness of intracoronary adenosine administration during primary PCI in STEMI patients with various methods and our study is in the same line. In one study, intracoronary adenosine infusion during PCI could significantly reduce the incidence of no-reflow phenomenon [23]. Furthermore, the patients who did not receive adenosine had a higher rate of in-hospital death. A similar study showed beneficial effects of intracoronary adenosine injection in preventing the no-reflow phenomenon, improving ventricular function, and enhancing clinical outcomes [24]. On the contrary, intracoronary bolus administration of 4 mg adenosine in STEMI patients did not have any effect on TIMI flow grade, TIMI frame count, and MBG following primary PCI [25]. In fact, not giving adenosine before reperfusion, and not treating all the patients within the first 3–4 h after STEMI event limits

In the multivariable logistic regression model and after adjustment for glycoprotein IIb/IIIa inhibitor, balloon post-dilation and their interaction, the protective effect of adenosine on new reflow (based on all three definitions) remained significant (p < .001 for all; Table 3).

### Discussion

This study showed that bolus intracoronary adenosine administration could effectively prevent no-reflow phenomenon in STEMI patients who underwent primary PCI, as detected by TIMI flow grade, MBG, and TIMI frame count. This effect remained significant after adjustment for confounding variables. Moreover, balloon post-dilation was less used in adenosine recipients.

Despite the successful use of primary PCI in the treatment of STEMI patients, the no-reflow phenomenon still has a noteworthy incidence [19]. Four mechanisms have been suggested for the development of no-reflow phenomenon: (1) distal atherothrombotic embolization; (2) ischemic injury; (3) reperfusion injury; (4) vulnerability of coronary microcirculation to injury [20]. Accordingly, various strategies have been undertaken to prevent the no-reflow phenomenon. Adenosine, mostly known by its potent vasodilator effect, also has anti-inflammatory and antiplatelet effects [21]. Therefore, it has appeared as an effective drug in the prevention of no-reflow phenomenon.

| Table 1. Comparison of the baseline characteristics of the study groups. |
|---------------------------------------------------------------|
| **Characteristic** | **Control Group (n = 118)** | **Intervention group (n = 110)** | **p-value** |
| Age, year          | 60 ± 12                      | 57 ± 11                        | .082       |
| Male gender, n (%) | 89 (75)                      | 92 (84)                        | .142       |
| Diabetes mellitus, n (%) | 22 (19)                      | 24 (22)                        | .621       |
| Dyslipidemia, n (%) | 23 (19)                      | 18 (16)                        | .606       |
| Hypertension, n (%) | 42 (36)                      | 32 (29)                        | .324       |
| Smoking, n (%)     | 45 (38)                      | 47 (43)                        | .502       |
| Creatinine, mmol/L | 0.10 ± 0.04                  | 0.10 ± 0.04                    | .557       |
| Glomerular filtration rate, ml.min/1.73m² | 72.4 ± 25.1 | 70.0 ± 20.8 | .422       |

Continuous variables are shown as mean (standard deviation), while categorical variables are shown as frequency (percentage). p < .05 was considered as statistically significant.

| Table 2. Comparison of the angiographic and angioplastich characteristics between the study groups. |
|---------------------------------------------------------------|
| **Characteristic** | **Control Group (n = 118)** | **Intervention group (n = 110)** | **p-value** |
| Culprit vessel, n (%) |                             |                               | .873       |
| LAD                 | 62 (52)                     | 54 (49)                       |            |
| LCX                 | 17 (14)                     | 17 (15)                       |            |
| RCA                 | 39 (33)                     | 39 (35)                       |            |
| Balloon pre-dilation, n (%) | 88 (74)                 | 77 (70)                       | .462       |
| Balloon post-dilation, n (%) | 59 (50)                 | 38 (34)                       | .023       |
| Glycoprotein IIb/IIIa inhibitor, n (%) | 94 (80)             | 100 (91)                      | .025       |
| Thrombus suction, n (%) | 20 (17)                    | 10 (9)                        | .116       |
| No-reflow based on TIMI flow grade, n (%) | 41 (35)                  | 15 (14)                       | <.001      |
| No-reflow based on MBG, n (%) | 63 (53)                 | 23 (21)                       | <.001      |
| No-reflow based on TIMI frame count, n (%) | 50 (42)                 | 16 (14)                       | <.001      |

p < .05 was considered as statistically significant.

| Table 3. Adjusted effect of intracoronary adenosine administration on the no-reflow phenomenon. Variables included in the model were age, glycoprotein IIb/IIIa inhibitor, balloon post-dilation, and their interaction. |
|---------------------------------------------------------------|
| **No-reflow** | **Odds ratio** | **95% confidence interval** | **p-value** |
| No-reflow based on TIMI flow grade | 0.272 | 0.136–0.542 | <.001 |
| No-reflow based on MBG | 0.250 | 0.136–0.460 | <.001 |
| No-reflow based on TIMI frame count | 0.233 | 0.120–0.453 | <.001 |

MBG: Myocardial blush grade; TIMI: Thrombolysis in myocardial infarction. p < .05 was considered statistically significant.
these findings and their interpretation. Likewise, AMISTAD-II study randomized 118 patients with evolving anterior STEMI receiving thrombolysis or primary PCI to a 3-h intravenous infusion of either adenosine or placebo [26]. The investigators observed no difference in the primary endpoint (new congestive heart failure beginning >24 h after randomization, the first re-hospitalization for CHF, or death from any cause within six months) between the two groups. Therefore, it seems that intravenous adenosine is not much effective in improving the clinical outcomes following PCI in STEMI patients. In another study in Turkey, intracoronary adenosine could not decrease the incidence of the no-reflow phenomenon as compared with intracoronary verapamil or placebo [27]. However, this study had a small population, and only 16 patients were treated with adenosine. This emphasizes our findings as we have used a bolus dose of adenosine and could reduce the rate of no-reflow phenomenon in our intervention group. A meta-analysis in which adenosine was compared with placebo showed a significant reduction of post-procedural no-reflow considering the STEMI population only. However, at a median follow-up of 6 months, preceding treatment with adenosine did not lead to clinical benefits in terms of reduction of mortality recurrent myocardial infarction, symptoms of heart failure or ST-resolution [28]. Nonetheless, not all the included studies used intracoronary adenosine and the study samples were too small. Therefore, an updated meta-analysis, considering our findings as well, can influence the current recommendations.

In our study, the frequency of balloon post-dilation was higher in the control group, whereas more patients in the intervention group received glycoprotein IIb/IIIa. Therefore, one might claim these differences might have been the reason for a lower no-reflow phenomenon in the intervention group. In order to remove the effect of these extraneous determinants, we used an adjustment model, which showed an independent effect of adenosine on reducing the no-reflow phenomenon.

In general, although studies that successfully used adenosine in STEMI patients undergoing primary PCI to prevent no-reflow are not few, there is still an argument about its effectiveness due to inconsistency between the studies and their limited number [9]. Therefore, as we showed that intracoronary adenosine could prevent no-reflow phenomenon in primary PCI following STEMI, the exact role of adenosine in this setting can now be defined more clearly and it can be introduced as a feasible treatment method. Nonetheless, other clinical benefits of adenosine, such as its effect on ejection fraction and major adverse cardiac events still need to be investigated.

The strengths of our results include its large number of participants, precise randomization, use of bolus dose of adenosine, execution of the PCI procedure by a single operator, and use of different methods to assess no-reflow phenomenon. However, we also have some limitations. First, this was a single-center study performed in a university hospital, so the external validity of our findings needs approval. Second, we only studied the incidence of the no-reflow phenomenon and did not evaluate other characteristics such as ejection fraction, infarct size, and level biomarkers. Several potential cofounders could influence our results. However, data were not available for some of these cofounders, such as time from pain onset to revascularization, medications, and past medical history. Therefore, we could not include them in our statistical model. Furthermore, we did not follow the patients for the development of major adverse cardiac events and long-term clinical outcome. Finally, we did not use a placebo, and the study was not blinded to the operator, although the patients and the statistician were unaware of the study groups.

Conclusion
Based on our findings and report of previous studies, intracoronary adenosine can be used effectively to prevent the no-reflow phenomenon in STEMI patients who are treated by primary PCI. This effect remained significant after adjustment for extraneous determinants. The routine use of adenosine in other patients who undergo PCI and its effect on clinical outcomes demands further study.

Disclosure statement
No potential conflict of interest was reported by the author(s).

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