Original Article

Intracoronary Adenosine to Prevent Myonecrosis in Patients with Stable Angina Undergoing Percutaneous Interventions: A Double-Blinded Randomized Controlled Trial

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Abstract

Background: *Significant elevation of cardiac biomarkers after percutaneous coronary intervention (PCI) is associated with increased mortality. However, clinical importance of lesser degrees of cardiac enzyme elevation has not been well understood. Multiple factors might have an etiologic role, and the incidence of myonecrosis has not changed dramatically despite pharmacological and technological advances in PCI. The aim of this study was to evaluate the role of intracoronary (IC) Adenosine in preventing the elevation of cardiac enzymes as a marker of myonecrosis after PCI in patients with chronic stable angina.*

Methods: *Two hundred sixty patients with chronic stable angina who were candidates for PCI were randomly assigned to double-blinded pretreatment with IC Adenosine or placebo before crossing of the guide wire. The patients were observed during the hospital course, and blood samples were obtained in standard intervals after the intervention for cardiac biomarkers. The primary end point of this study was post-PCI myonecrosis, and secondary end point was safety of IC Adenosine administration in the setting of PCI in patients with chronic stable angina.*

Results: *Of the 260 patients, who were initially randomized, finally 83 patients were analyzed in the placebo and 96 in the Adenosine arms. The study patients were comparable in clinical and angiographic characteristics. The mean of the patients' age was 57.3 years (range = 35 to 79 years), and 71.5% were male. There were no differences in the mean serum cardiac biomarkers between the study groups (mean creatine kinase-MB [CK.MB] level of 29.5 ± 14.5 IU/L in the placebo group and 31.5 ± 18.5 IU/L in the control group; p value = 0.41; mean cardiac troponin I (cTnI) level of 0.097 ± 0.178 µg/L in the placebo group and 0.167 ± 0.5 µg/L in the control group; p value = 0.24).*

Conclusion: *Despite promising results in primary PCI, our study showed that a strategy of IC Adenosine pretreatment is not beneficial in reducing post-PCI myonecrosis in patients with chronic stable angina and should not be routinely used.*

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Introduction

Percutaneous coronary intervention (PCI) is superior to medical therapy in relieving symptoms in many patients with stable angina.[1, 2] Relief of symptoms is both more rapid and complete with PCI than it is with medical treatment, although long-term survival may not change significantly in a large subset of patients.[1, 3, 4] Patients with large objective ischemia might benefit from PCI in terms of mortality reduction. Since the advent of coronary stents, success rates have increased and the outcomes of angioplasty procedures have improved. Nevertheless, the incidence of cardiac enzyme elevation has not changed significantly.[5, 6] Different studies have revealed that cardiac enzyme rising after PCI might be associated with increased mid- and long-term mortality.[7-12] Possible causes of cardiac enzyme elevation after PCI are distal embolization of thrombotic or atherosclerotic debris, platelet activation and thrombus formation, neurohormonal activation, microvascular spasm, oxidative stresses, inflammation, and occlusion of a side-branch at the site of angioplasty.[13-18] Many strategies have been introduced to prevent this phenomenon, including medical and interventional therapies. Antiplatelet and lipid-lowering therapies, anticoagulation, and the use of direct stenting are some of the proposed strategies.[19-22]

Adenosine with the activation of vascular smooth cell A2-receptors dilates coronary arteries in an action that is not endothelial-dependent. The effects are more relevant on the vessels smaller than 100 μm; and, hypothetically, it can prevent myonecrosis with preconditioning and improve microcirculation during ischemic episods.[23, 24] Several studies have shown the beneficial effects of intracoronary (IC) Adenosine in the setting of primary PCI in patients with ST-elevation myocardial infarction (STEMI) in terms of reducing no-reflow, infarct size, and mortality.[25-27] Until now, patients with chronic stable angina have not been addressed in the studies. The aim of the present study was to evaluate the effect of prophylactic IC Adenosine in preventing the elevation of cardiac enzymes as a marker of myonecrosis after PCI in patients with stable angina.

Methods

This is single-center trial with a prospective design of stable angina patients undergoing PCI. The study population was randomized to double-blind treatment with placebo or IC Adenosine, with parallel design and allocation ratio of 1:1. The institutional Ethics Committee of the hospital approved the trial design.

Five hundred patients were initially evaluated between September 2009 and October 2010. Patients were considered eligible if they were older than 18 years of age, with chronic stable angina and indication for PCI because of drug-refractory chest pain or documented intermediate to high-risk ischemia on non-invasive tests.

Exclusion criteria were a history of allergic reaction to Adenosine or the presence of asthma; cardiogenic shock at the time of treatment; myocardial infarction (MI) or unstable angina within the previous month; left main stenosis; total coronary occlusion; in-stent restenosis; interventions on saphenous vein grafts (SVG); untreated major complications during PCI including sub-occlusive or occlusive dissection, perforation, or large side-branch (SB) loss (SB diameter > 2 mm with > 80% stenosis or thrombolysis in myocardial infarction (TIMI) flow < 3); visible thrombosis; plain old balloon angioplasty; use of atherectomy or rotablation devices; administration of a glycoprotein IIb/IIIa inhibitor; second- or third-degree heart block in the absence of pacemaker; increased cardiac enzymes in the baseline; acute or chronic renal failure (creatinine > 2 mg/dl); contraindication to Aspirin or Clopidogrel; bleeding tendency; and pregnancy.

The sample size was determined through a power analysis process based on the results of similar studies.[5] Using the Z approximation formula for the sample size calculation and considering a myonecrosis prevalence of 10% for Adenosine-treated patients, and 30% for placebo ($\alpha = 0.05$, $\beta = 0.1$), the sample size was calculated as 84 persons in each group. All the patients provided written informed consent before randomization.

The patients received Aspirin, 300 mg loading dose of Clopidogrel, and a statin before the procedure. The femoral artery access was obtained, and the coronary anatomy of the patients was evaluated by performing selective coronary angiography or reviewing the previous angiogram. Intention to treat was for a seemingly culprit lesion or lesions based on non-invasive measures and angiographic features. Heparin was administered with the dose of 100 IU/kg to maintain an activated clotting time > 250 s.

Randomization was performed based on the computerized balanced block randomization method in blocks of four. Randomization concealment was carried out via the sealed envelope technique. Eligible patients were allocated in a ratio of 1:1 to one of two arms. IC Adenosine was administered after the engagement of the guiding catheter and before guide wire crossing. The interventional procedures were in accordance to the routine guidelines. The operators tried to do direct stenting if it was possible. If not, the strategy of

pre-dilatation and stenting was chosen. Selection of a bare-metal or drug-eluting stent was according to the clinical and angiographic characteristics and considering financial limitations.

The patients were observed during the hospital course, and their clinical status was recorded. Blood samples were obtained 8, 16, and 24 hours after the intervention for creatine kinase-MB (CK.MB), and after 12 hours for cardiac troponin I (cTnI). The levels above the cut-off points were considered the markers of myonecrosis.

Stability of Adenosine in various diluents, including 5% dextrose, 0.9% sodium chloride, and lactated Ringer, has been previously shown when prepared in polypropylene syringes and polyvinyl chloride (PVC) bags.[28] We administered 120 µg of Adenosine, diluted in 20 cc saline for the left coronary intervention, and 60 µg, diluted in 10 cc saline, for the right coronary intervention as a bolus shot via the guiding catheter. Given that Adenosine diluents are colorless, 20 cc of saline was administered for the left coronary and 10 cc, for the right coronary interventions to obtain treatment concealment in the comparison groups. Doses of Adenosine were selected after the review of studies with a similar design.

The primary efficacy outcome of this study was post-PCI myonecrosis, defined as an elevation in CK.MB greater than the upper limit of normal (> 25 IU/L) or a maximum cTnI equal to or greater than 0.01 µg/L. Secondary end point was safety of IC Adenosine administration in the setting of PCI in patients with chronic stable angina.

The data are described as mean ± standard deviation for the interval and count (per cent) for the categorical variables. The analyses were performed according to the intension to treat (ITT) approach. The interval variables with normal distribution were compared using the Student t-test between the two groups. The interval variables without normal distribution and ordinal variables were compared using the Mann-Whitney U test. The chi square or Fisher exact test was used to compare the nominal data between the study groups. A p value < 0.05 was considered statistically significant.

Adjusted associations between the high serum enzyme levels and the other determinants were investigated with logistic regression models, using the backward conditional method.

SPSS 15 ® for Windows ® (SPSS Inc., Chicago, Illinois) was applied for the statistical analyses.

Results

Among the 500 patients, who were initially evaluated, 260 patients underwent random assignment: 130 to IC Adenosine and 130 to placebo (Figure 1). Forty-seven patients were censored from the placebo group and 34 from the Adenosine group because of randomization error or loss of follow-up. Finally, 83 patients were analyzed in the placebo and 96 in the Adenosine arms.

The study patients were comparable in terms of clinical

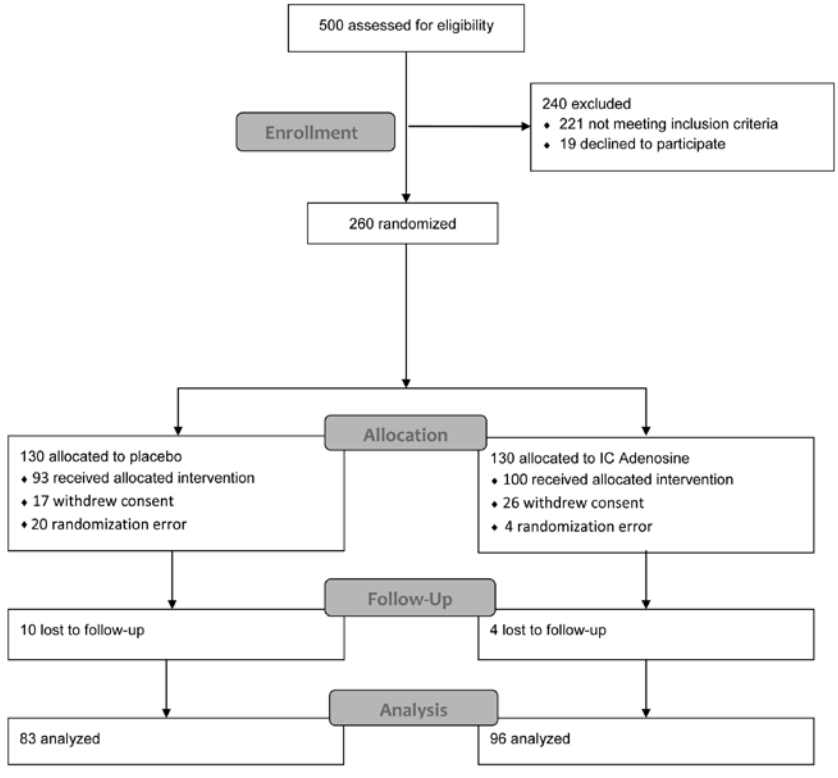

Figure 1. Flow chart of the participants

Table 1. The characteristics of the patients*

	Placebo Group (n=83)	Adenosine Group (n=96)	P value
Age (y)	56.77±9.5	57.78±10.1	0.28
Sex			0.15
Male	55 (66.3)	73 (76.0)	
Female	28 (33.7)	23 (24.0)	
Risk Factors			
Smoking	23 (27.7)	28 (29.2)	0.83
Hypertension	39 (47.0)	41 (42.7)	0.21
Dyslipidemia	58 (69.9)	66 (68.8)	0.87
Diabetes	36 (43.4)	33 (34.0)	0.56
Family history	10 (12.0)	13 (13.5)	0.76
Renal dysfunction**	10 (12.0)	16 (16.7)	0.38
Previous MI	22 (26.5)	36 (37.5)	0.12
Previous PCI	10 (12.0)	8 (8.3)	0.41
Left ventricular function			0.15
Normal (EF > 50%)	56 (67.5)	49 (51.0)	
Mildly reduced (EF = 41-50%)	18 (21.7)	34 (35.4)	
Moderately reduced (EF = 31-40%)	6 (7.2)	10 (10.4)	
Severely reduced (EF ≤ 30%)	3 (3.6)	3 (3.2)	

*Data are presented as mean±SD or n (%)
**Renal dysfunction defined as serum creatinine more than 1.5 mg/dl
MI, Myocardial infarction; PCI, Percutaneous coronary intervention; EF, Ejection fraction

Table 2. Angiographic and procedural data*

	Placebo (n=83)	Adenosine (n=96)	P value
Target vessel			0.69
LAD	52 (62.7)	61 (63.5)	
LCX	9 (10.8)	13 (13.5)	
RCA	17 (20.5)	17 (17.7)	
Other	5 (6.0)	5 (5.2)	
Lesion type			0.47
A	16 (19.6)	15 (15.6)	
B	46 (55.4)	49 (51.0)	
C	21 (25.3)	32 (33.3)	
Bifurcation lesion	10 (12.0)	12 (12.5)	0.92
Severe tortuosity	3 (3.4)	3 (3.1)	0.85
Heavy calcification	3 (3.7)	6 (6.2)	0.50
Lesion location			0.61
Ostial	1 (1.2)	3 (3.1)	
Proximal	37 (44.6)	35 (36.5)	
Mid-part	41 (49.4)	52 (54.2)	
Distal	4 (4.8)	16 (6.3)	
Angioplasty procedure			
Pre-dilation	23 (28)	33 (34.4)	0.43
Post-dilation	21 (25.6)	33 (34.4)	0.18
Number of stents			0.97
1	71 (86.6)	84 (87.5)	
2	8 (9.8)	9 (9.4)	
3	3 (3.7)	3 (3.1)	
Multi-vessel stenting	20. (24.6)	15 (15.1)	0.15
Mean stent length (mm)	20.8±8.2	21.9±7.9	0.35
Stent type			0.5
Bare-metal	54 (65.1)	68 (70.8)	
Drug-eluting	26 (31.3)	23 (24)	
Both	3 (3.6)	5 (5.2)	
Procedural complications			0.17
Side branch involvement**	2 (2.4)	9 (9.4)	
Side branch occlusion***	1 (1.2)	1 (1.0)	
Subtotal/total dissection	1 (1.2)	1(1.0)	
Slow/no-reflow	1 (1.2)	0	
Coronary perforation	0	1 (1.0)	

*Data are presented as mean±SD or n (%)
**Side branch (SB) involvement defined as 50-80% stenosis of ostial SB with thrombolysis in myocardial infarction (TIMI)-3 after stenting
***SB occlusion defined as > 80% stenosis of ostial SB or TIMI ≤ 2 after stenting
LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery

and angiographic characteristics (Tables 1 and 2). The mean of the patients' age was 57.3 years (range = 35 to 79 years), and 71.5% were male. Dyslipidemia was the most common risk factor (69.3%), and a relatively high number of the study patients suffered from diabetes mellitus (38.5%). Ten per cent of the patients had a history of prior PCI and 32.4% a history of MI. The left anterior descending (LAD), right coronary artery (RCA), and left circumflex (LCX) were treated in 63, 19.6, and 12%, respectively. The most treated lesions were of type B (53.1%) (according to the American College of Cardiology/American Heart Association's guideline for percutaneous coronary angioplasty),[29] located at the proximal to mid-part of the arteries.

Of note, fewer than 20% of the lesions had a complex anatomy, including bifurcational site, heavy calcification, and severe tortuosity. If possible, direct stenting was the intended strategy in most (68.2%) patients. Two-hundred seven stents were implanted (1.15 stents per patient), and multi-vessel stenting was done in 35 (19.6%) patients. Bare-metal stents (72%) were mostly utilized, and a combined stenting strategy using both bare-metal and drug-eluting stents was adopted in 8 (4.4%) patients.

Procedural complications were equally distributed in the two groups. Excluding the SB involvement, defined as 50 to 80% stenosis of the SB ostium with TIMI flow-3, complications were rare (3.6% in the placebo vs. 3% in the Adenosine group), as is shown in Table 2. Complications were equally distributed in the study patients (p value = 0.17).

The percentages of the patients in the Adenosine or placebo groups who had positive CK.MB and cTnI levels regarding the cut-off values are presented in Table 3. The mean CK.MB level was 29.5 ± 14.5 IU/L in the placebo group and 31.5 ± 18.5 IU/L in the control group, without a significant statistical difference (p value = 0.41). The mean cTnI level was 0.097 ± 0.178 µg/L in the placebo group and 0.167 ± 0.500 µg/L in the control group, without a significant statistical difference (p value = 0.24). Figures 2 and 3 show the comparisons of the mean serum CK.MB and cTnI between the study groups. Multivariate analysis did not reveal any associations between the high serum enzyme levels and clinical, angiographic, and procedural determinants.

IC Adenosine was safe and without permanent complications. Only, two patients experienced significant sinus bradycardia and complete heart block, which were transient and resolved spontaneously within seconds.

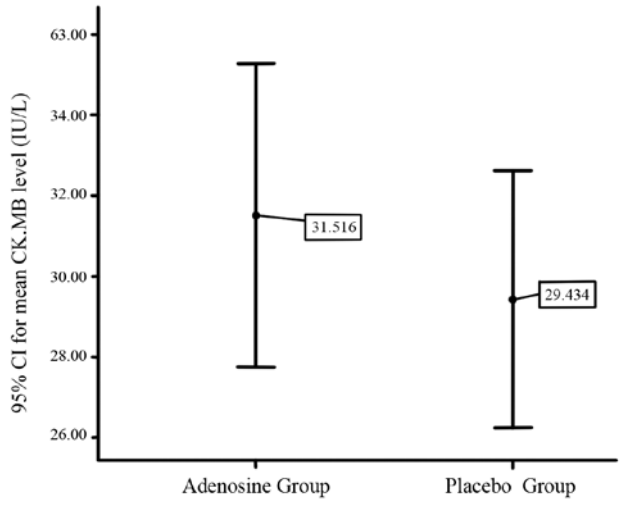

Figure 2. Comparison of the mean serum creatine kinase-MB (CK.MB) levels between the study groups

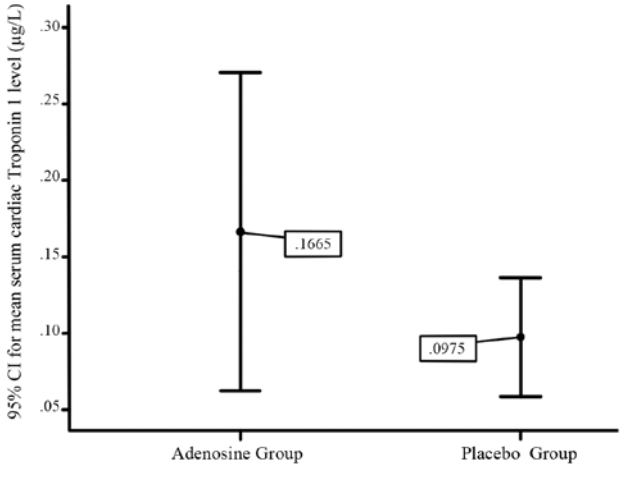

Figure 3. Comparison of the mean serum troponin I levels between the study groups

Table 3. Cardiac biomarkers in the study patients*

Group	Positive CK.MB**	CK.MB Level (IU/L)	Positive cTnI***	cTnI level (µg/L)
All patients	92 (52)	30.4±16.7	57 (32.2)	0.134±0.390
Adenosine	51 (54.3)	31.5±18.5	28 (29.8)	0.167±0.500
Placebo	41 (49.4)	29.5±14.6	29 (34.9)	0.097±0.178
P value	0.77	0.41	0.47	0.24

*Data are presented as mean±SD or n (%)
**Positive creatine kinase-MB (CK.MB) defined as elevation in CK.MB > 25 IU/L
***Positive cardiac troponin I (cTnI) defined as elevation in cTnI ≥ 0.01 µg/L

Discussion

PCI is indicated in many patients with stable coronary artery disease (CAD) because of refractory angina and severe ischemia detected on non-invasive tests and might improve symptoms and survival in some cases. In spite of a very low prevalence in stable CAD, no-reflow phenomenon is the most feared complication of PCI. Current data have reported an incidence of 0.6 to 2 % for all PCI types. There is higher risk during primary PCI, PCI on SVGs, and rotational atherectomy. Several key pathophysiological processes, usually in combination, are believed to be responsible for this complication such as distal embolization of atherothrombotic debris, thrombus formation, and endothelial dysfunction of the distal arteriolar and capillary bed, including endothelial desquamation and microcirculatory vasospasm. It can lead to myonecrosis, elevation of cardiac enzymes, and increased long-term mortality.

At least theoretically, intracoronary administration of Adenosine might prevent myonecrosis from the slow/no-reflow following microvascular spasm and currently is frequently used as its treatment following PCI. The effects of Adenosine have been shown in both animal models[30] and clinical studies.[25, 31-33] The beneficial effects seem to be because of a combination of distal vasodilatation, decrease in neutrophil count, and preservation of the endothelial structure. The majority of studies have evaluated IC Adenosine as a treatment or prophylaxis in the setting of primary PCI or SVG intervention, and only a few have addressed patients with chronic stable angina. Unlike primary PCI patients, our study demonstrated no protective effect for IC Adenosine during PCI in stable angina patients. The possible explanations might be a low incidence of myonecrosis in the study patients and the small sample size of our study, which was not sufficiently powered to reveal the associations. Other possible causes of myonecrosis are SB involvement and distal embolization, which do not reverse with Adenosine; use of cardiac enzymes, as the only marker of myonecrosis and no-reflow; and very short half-life of Adenosine, which can lead to a decrease in the effective concentrations of Adenosine at the time of stenting. We also used small doses of Adenosine compared with some other studies, which can be a limiting factor.

First and foremost among the limitations of the present study is that it is not sufficiently powered because of the small number of participants. In addition, there might be other factors which can lead to the release of cardiac biomarkers such as contrast injection, catheter manipulations, and distal embolism of the air and microscopic particles.

Conclusion

In conclusion, the data derived from our study suggest that IC Adenosine probably does not prevent myonecrosis in stable CAD patients undergoing PCI and should not be used routinely during PCI in stable patients. Be that as it may, Adenosine is still an important therapeutic option after the occurrence of the no-reflow phenomenon.

Acknowledgment

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