The Comparison of Intracoronary Versus Intravenous Eptifibatide Administration during Primary Percutaneous Coronary Intervention of Acute ST-Segment Elevation Myocardial Infarction

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Abstract: Background: Administration of the glycoprotein IIb/IIIa inhibitors, including eptifibatide is an effective adjunctive treatment strategy during primary percutaneous coronary intervention (PPCI) for ST-segment elevation myocardial infarction. Recent data suggest that the intracoronary administration of these drugs during PPCI may increase the efficacy of them. **Methods:** A total of 40 ST-segment elevation myocardial infarction patients undergoing PPCI within 12 hours of symptom onset were randomized to either intracoronary or intravenous two boluses of eptifibatide (0.180 µg/kg) each 10 minutes. The primary endpoints of the trial were enzymatic infarct size, myocardial reperfusion measured as ST-segment resolution (STR), and post-procedural Thrombolysis in Myocardial Infarction (TIMI) grade flow of infarct related artery. The secondary endpoints were intra-procedural adverse effect (arrhythmia) and no-reflow phenomenon, in-hospital mortality, reinfarction , hemorrhage and post-procedural global systolic function. **Results:** Post-procedural TIMI grade 3 flow was achieved in 95% and 90% of the intracoronary (IC) and intravenous (IV) groups (P=0.61). The enzymatic infarct size assessed by the area under the curve of creatine phosphokinase-mb (CPK-mb) in the first 48 hours after PPCI ($\mu mol.L^{-1}.h^{-1}$) was similar in the IC and IV groups with 7206 (IQR, 5346.75 to 10384.50) versus 7294 (IQR , 10384.50 to 10384.50), P=0.87. Complete STR was achieved in 55% and 40% of the IC and IV groups (P=0.27). No deaths, urgent revascularizations, reinfarctions, or TIMI major bleeding events were observed among the both groups. **Conclusion:** Although, the IC administration of eptifibatide is safe, but does not add a benefit in comparison to the standard IV route.

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Keywords: Primary percutaneous coronary intervention, ST elevation myocardial infarction, Eptifibatide, Intracoronary, Intravenous.

Introduction

Primary percutaneous coronary intervention (PCI) is the treatment of choice in the management of acute ST-segment elevation myocardial infarction (STEMI). It has been constantly observed that, despite restoring good epicardial flow with PCI, myocardial perfusion at the cellular level remains impaired in nearly 50 % of STEMI patients.[1] This is attributable to embolisation of the coronary thrombus into the distal vasculature, producing microvascular plugging, vasospasm, interstitial oedema and cellular injury. With Doppler guidewire technology, it was estimated that an average of 25 embolic events occurred during primary PCI for ST-segment elevation myocardial infarction. [2,3,4] There is consequently less salvage of infarct size, reduced left ventricular function and poorer clinical outcomes. There have been efforts to identify mechanical and pharmacological strategies to improve myocardial perfusion after primary PCI. Compared with systemic administration of intravenous pharmacotherapies, highly localized administration of intracoronary pharmacotherapy may be associated with a several-hundred-fold increase in the local concentration of an agent in the epicardial artery and microcirculation. A number of pharmacotherapies, including adenosine[5,6], calcium channel blockers[7], vasodilators[8,9],

antithrombotics[10,11], and antiplatelet[12-14] agents have been used to treat microvascular dysfunction.

This led to the development of a new class of antiplatelet drugs, termed glycoprotein IIb/IIIa inhibitors (GPIs), which are the most potent inhibitors of platelet aggregation and have been repeatedly shown to improve clinical outcomes in acute STEMI when administered intravenously during primary PCI. [15]

Platelet receptor occupancy studies have demonstrated that if there are fewer GPIIb/IIIa receptors free and available for cross-linking with fibrinogen, then myocardial perfusion is improved. [16] In recent years, randomized trials have demonstrated that glycoprotein inhibitors administered by the intracoronary route are safe and effective in reducing infarct size and providing better clinical outcomes than when given intravenously, without a significant increase in major bleeding. [14, 15]There were no adverse events during its administration. The intracoronary strategy was not associated with any significant delay in revascularization compared with the intravenous route. [14]

The absolute number of GPIIb/IIIa receptors available for cross-linking is reduced among patients with successful restoration of myocardial perfusion and ST-segment resolution in an STEMI population. [17] Thus, the hypothesized mechanistic basis for intracoronary administration of GPIIb/ IIIa inhibitors is that high local concentrations of the drug would lead to fewer GPIIb/IIIa receptors being available for cross-linking with fibrinogen in the coronary microcirculation and therefore promote clot disaggregation with a minimal increase in systemic drug concentrations. This greater blockade of GPIIb/IIIa receptors would in turn reduce the incidence of microcirculatory thrombosis, improve myocardial perfusion, and ultimately improve clinical outcomes. [14, 16]

Table 1. Baseline Characteristics of the 40 Patients Randomized To Intracoronary or Intravenous Administration Of Eptifibatide.

Patients' baseline characteristics	Intracoronary Group (n=20)	Intravenous Group (n=20)	P
Age (year)	53.9±10.6	58.60±7.0	NS
Male gender, n (%)	17 (34.7)	17 (34.7)	NS
Cardiovascular risk factors, n (%)			
Hypertension, n (%)	4 (20)	5 (25)	NS
Hypercholesterolemia, n (%)	5 (25)	6 (30)	NS
Diabetes mellitus, n (%)	9 (45)	6 (30)	NS
Family History, n (%)	4 (25)	2 (10)	NS
Smoking, n (%)	11 (55)	11 (55)	NS
Ischemic time(min)			NS
Angiographic, n (%)			
No. of diseased vessels			
1	8 (40)	8 (40)	NS
2	7 (35)	5 (25)	NS
3	5 (25)	7 (35)	NS
Infarct-related artery			
LAD	14 (70)	11 (55)	NS
LCX	1 (5)	0	NS
RCA	5 (25)	9 (45)	NS
TIMI flow grade, n (%)			
0	18 (90)	17 (85)	NS
1	2 (10)	2 (10)	NS
2	0	1 (5)	NS
3	0	0	NS
Thrombus present, n (%)	18 (90)	19 (95)	NS
Procedural, n (%)			
Thrombus aspiration	15 (75)	13 (65)	NS
Balloon predilatation	10 (50)	9 (45)	NS
Postdilatation	13 (65)	12 (60)	NS
DES	12 (60)	14 (70)	NS

DES: Drug Eluting Stent

We hypothesized that intracoronary administration of eptifibatide during primary PCI for ST-elevation myocardial infarction would be safe and would be associated with higher rates of myocardial reperfusion and smaller myocardial infarct size.

Patients and Methods

Study Design and Population

In the present study, the investigators randomized 40 STEMI patients, presenting within 12 hours of symptom onset, to either intracoronary or intravenous two boluses of eptifibatide. STEMI was defined as chest pain suggestive of myocardial ischemia for at least 30 minutes before hospital admission, and an ECG with new ST-segment elevation in 2 or more contiguous leads of 0.2 mV or more in leads V2 to V3 and/or 0.1 mV or more in other leads. The use of this drug was strongly encouraged based on the existing guidelines.

The exclusion criteria were as below:

1- Patients presenting with STEMI after 12 hours from symptoms onset.

2- Patients presenting with vasospastic angina (determined by resolution of ST segment elevation, and relief of symptoms after intravenous administration of nitroglycerin).

3 -Patients presenting with non-STEMI.

4-Contraindications for antiplatelets such as bleeding disorder including gastrointestinal bleeding, hematuria, or known any bleeding tendency either inherited or acquired.

5- Thrombocytopenia (Platelet count<100.000/cm3).

6- Recent (<6 months) Stroke.

7- Intracranial hemorrhage at any time in patient's life or any known intracranial malformation.

8- Cardiogenic shock.

9- LBBB change in ECG.

Patients' baseline characteristics are listed in Table 1.

Treatment

All patients received 325 mg of acetylsalicylic acid orally and a 600-mg loading dose of clopidogrel 30- 60 minutes before PCI. And a maintenance dose of 75 mg/day for 4 weeks to one year were administered after PCI. A bolus and a maintenance dose of unfractionated heparin were administered and titrated to achieve an activated clotting time 250 seconds.

Two boluses (each 180 μg/kg) of eptifibatide were administered in both groups. Coronary guiding catheters were used to administer intracoronary eptifibatide. When the wire had crossed the occlusion, the first dose was administered, and after 10 minutes the patient was received the second dose. Thrombus aspiration was performed using Export catheter, if it was necessary. Stenting was performed for all of the patients. Intra-aortic balloon pump (IABP) was not used for any patient.

End Points

The primary endpoints of the trial were enzymatic infarct size, myocardial reperfusion measured as ST-segment resolution (STR), and post-procedural TIMI grade flow the infarct-related artery. The secondary endpoints were intra-procedural adverse effect (arrhythmia) and no-reflow phenomenon, in-hospital mortality, reinfarction and hemorrhage (major or minor) using TIMI criteria, and post-procedural global left ventricular systolic function, using global ejection fraction.

ECG Analysis

For evaluation of the ECG end points, a 12-lead ECG was acquired at the time of presentation and at 90 minutes after primary PCI. STR was assessed by comparing the ST-segment elevation in the infarct-related area on the ECG after PCI with the ECG at presentation.STR indirectly indicates the myocardial reperfusion. In our study, STR was categorized as complete (≥70%), partial (30% to <70%), or absent (<30%).[18]

Infarct Size

The infarct size was measured indirectly by the area under the curve of the cardiac creatine kinase-mb (CPK-mb) release, derived from measurements 0, 6, 24 and 48 hours after PCI.

Angiographic Analysis

"TIMI Grade Flow" is a scoring system from 0-3 referring to levels of coronary blood flow assessed during percutaneous coronary angioplasty:

- TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond a coronary occlusion.
- TIMI 1 flow (penetration without perfusion) is faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed.
- TIMI 2 flow (partial reperfusion) is delayed or sluggish antegrade flow with complete filling of the distal territory
- TIMI 3 flow (complete perfusion) is normal flow which fills the distal coronary bed completely. [19]

A single observer reviewed all angiographic and ECG data.

In-hospital Clinical Course

In-hospital clinical course was obtained from the central personal records database, hospital records, and interviews with the patients and/or their general practitioners. Mortality was considered cardiac unless an unequivocal noncardiac cause of death was established. Reinfarction was defined as recurrent symptoms suggestive of ischemia with new ST-segment elevation and/or elevation of the levels of cardiac markers. [20]

Major or minor hemorrhage was determined using Thrombolysis In Myocardial Infarction (TIMI) criteria, including:

A) Major criteria: intracranial hemorrhage, or clinical bleeding associated with loss of >5 mg% of hemoglobin (or hematocrit decrease by > 15 points or by 10-15 points with clinical bleeding).

B) Minor criteria: loss of > 3gm% of hemoglobin (or hematocrit decrease by < 10 points) with clinical bleeding or loss of > 4 mg% of hemoglobin (or hematocrit decrease by 10- 15 points) with no clinical bleeding.

Clinical bleeding will be defined as: large hematoma, gastrointestinal blood loss, retroperitoneal bleeding.

All patients prior to discharge will undergo a conventional transthoracic echocardiographic examination (TTE), to assess the global left ventricle systolic function (LVEF) by 2D eyeballing approach.

Statistical Analysis

Due to the lack of normal distribution of data and small sample size in each group, quantitative data were described by median and inter-quartile range and compared by Mann-Whitney U test. Categorical data were described by frequencies and percentages and analyzed by chi square and Fisher exact test. AUC was calculated by trapezoidal rule. Significance level was determined at $P<0.05$. Statistical analyses were done by SPSS version 20.

Results

Angiographically apparent thrombus was noted in 95 (IV group) and 90 percent (IC group) of cases. More than 95% of arteries had a closed artery (TIMI grade 0/1 flow) before PCI, as noted in table 1. No deaths, urgent revascularizations, or reinfarctions were observed among the 40 patients of both groups. There were no TIMI major bleeding events. One TIMI minor bleeding events were noted in whom were treated with intracoronary eptifibatide. No adverse events including arrhythmias were noted during intracoronary eptifibatide administration.

Postprocedural TIMI grade 3 flow was achieved in 95% and 90% of the intracoronary and intravenous groups, respectively (*P*=0.61). (Table 2)

Table 2. Post-procedural TIMI flow grade of infarct related artery.

Post-procedural TIMI flow grade	Intracoronary Group (n=20)	Intravenous Group (n=20)	P
3, n(%)	19 (95)	18 (90)	0.61
2, n(%)	1 (5)	2 (10)	0.85

The enzymatic infarct size assessed by the area under the curve of CPK-mb in the first 48 hours after primary PCI ($\mu mol.L^{-1}.h^{-1}$) was similar in the intracoronary and intravenous groups with 7206 (IQR, 5346.75 to 10384.50) versus 7294 (IQR , 3797.25 to 11803.50), P=0.87. Also, the other enzymatic criteria were similar in the IC and IV groups: peak CPK-MB (U/L) was 277 (IQR, 187.75 to 498.75) versus 257.5 (IQR, 115 to 420), P=0.48; and time to peak CPK-MB (hour) was 6 (IQR, 6 to 16.5) and 6 (IQR, 6 to 12), P=0.84. (Table 3 and figure 1, 2, 3)

Median STR was 71% (inter-quartile range 40 to 72 %) in the intracoronary group versus 63.5% (inter-quartile range, 50 to 75%) in the intravenous group; *(P*=0.75). The primary end point of complete STR was achieved in 55% of the intracoronary group and 40% of the intravenous group (*P*=0.27). Therefore myocardial reperfusion was similar in both groups. (Table 4, and figure 4)

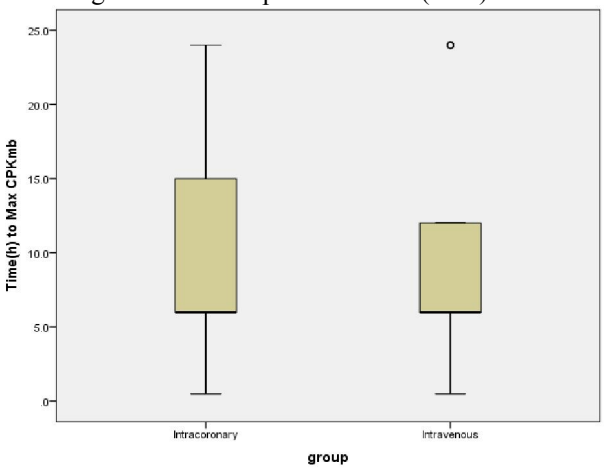
Global LV systolic function which assessed by ejection fraction (2D eyeballing approach) in transthoracic echocardiographic examination before discharge, was 45 % (inter-quartile range35 to 47.25 %) in the IC group versus 40 % (inter-quartile range, 38.5 to 45 %) in IV group; *(P*=0.21). (Table 5)

Table 3. Enzymatic Infarct Size in both groups.

	Intracoronary Group (n=20)	Intravenous Group (n=20)	P
Time to peak CPK-MB, h	6 (6 to 16.5)	6 (6 to 12)	0.84
Peak CPK-MB, U/L	277.0 (187.75 to 498.75)	257.5 (115 to 420)	0.48
AUC48 CPK-MB, $\mu mol.L^{-1}.h^{-1}$	7206 (5346.75 to 10384.50)	7294 (3797.25 to 11803.50)	0.87

AUC: Area under the Curve
CPK-mb: Creatine PhosphoKinase-mb

Figure 1. Time to peak CPK-mb (hour)



CPK-mb: Creatine Phosphkinase-mb

Figure 2. Infarct size according to Area under Curve (AUC) of CPK-mb during the first 48 hours after PCI

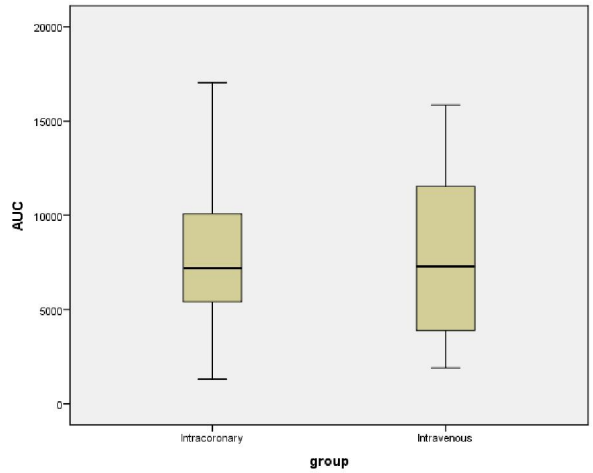
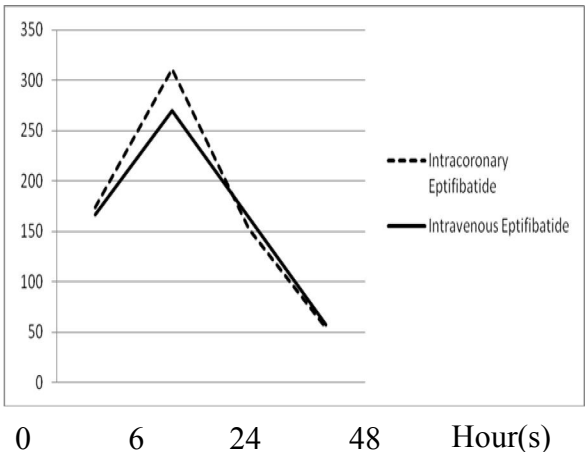


Figure 3. CPK-mb serum level changes the first 48 hours after PCI.



CPK-mb: Creatine Phosphokinase-mb

Table 4. Distribution of myocardial reperfusion as assessed by ST-segment resolution (STR)

Post-PCI STR	Intracoronary Group (n=20)	Intravenous Group (n=20)	P
Median	71 (40-72)	63.5 (50-75)	0.75
Mean ± SD	55.95± 25.7	61.35± 15.25	
Absent (<30%), n (%)	3 (15)	1 (5)	
Partial (30- <70 %), n (%)	6 (30)	11 (55)	
Complete (≥70 %), n (%)	11 (55)	8 (40)	0.27

STR: ST resolution

Figure 4. Distribution ST-segment resolution (STR)

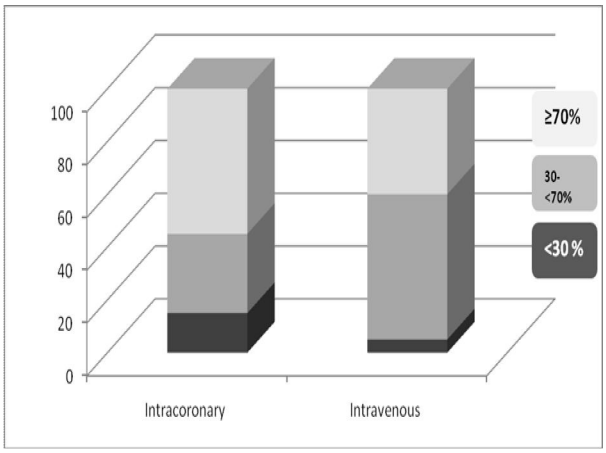


Table 5. Ejection fraction (EF) in both groups before discharge (P=0.21)

	Intracoronary Group (n=20)	Intravenous Group (n=20)
Median EF (%)	45 (35.0- 47.25)	40 (38.5- 45)
Mean EF (%)	40.80± 9.39	42.00± 5.876

EF: Ejection Fraction

Discussion

Mechanisms underlying impaired myocardial perfusion after restoration of epicardial blood flow are likely to be multifactorial such as oxygen free radicals, cellular and interstitial edema, endothelial dysfunction, vasoconstriction, and thromboembolism. [21,22] The increased concentration of Gp IIb/IIIa inhibitors like Abciximab, Eptifibatide, Tirofiban are shown to improve the outcomes of PCI safely and efficaciously in terms of reduction in infarct size, peri-procedural MI and improved TIMI flow. [16]

Depending on the relation of inflow and outflow and the size of the ischemic area, the local eptifibatid concentration can vary substantially. However, even in situations with restitution of normal flow and perfusion in the infarct-related artery, intracoronary drug bolus administration will result in very high local concentrations, which might be much higher than the usual intravenous application that might more reduces platelet aggregation. [23] Another potential mechanism of high local concentration benefits might be related to the anti-inflammatory properties of GP IIb/IIIa inhibitors. These considerations are supported by experimental data showing a dose-dependent platelet disaggregation. Concentrations that produced complete platelet disaggregation also induced partial displacement of platelet-bound fibrinogen, which might play a role in the clinical setting. [25]

The angiographic and electrocardiographic end points are well established for the assessment of perfusion at the epicardial and microvascular levels. The sensitive ECG assessment at a later measurement reflected improved tissue perfusion. [26]

In our study, the STEMI patients undergoing primary PCI, intracoronary administration of eptifibatide is not superior to intravenous administration, with respect to the primary endpoints: improving myocardial reperfusion as assessed by STR, the enzymatic infarct size measured by the area under the curve of CPK-mb in the first 48 hours after primary PCI, and post-procedural TIMI grade flow of infarct related artery.

The other findings of the present investigation were associated without significant differences in moderate and/or severe bleeding complications, deaths, urgent revascularizations, or reinfarctions, and adverse events (during intracoronary eptifibatide administration) including arrhythmias, between two groups.

Also we recognized that if balloon postdilation was necessary, it could be performed safely, with minimal risk of no-reflow phenomenon.

Recently the use of intracoronary versus intravenous was compared in some trials and studies; which had different results. For example, in CICERO (The Comparison of Intracoronary Versus Intravenous Abciximab Administration during Emergency Reperfusion of ST-Segment Elevation Myocardial Infarction) Trial, 534 patients of STEMI undergoing PPCI with thrombus aspiration within 12 hours of symptom onset, were randomized to either intracoronary or intravenous bolus of abciximab (0.25 mg/kg).No difference was noted in ST resolution between intracoronary versus intravenous groups. However, intracoronary administration was ssociated with improved myocardial perfusion assessed by myocardial blush grade and a smaller enzymatic infarct size. [18]

Similarly, in the Intracoronary Eptifibatide (ICE) Trial, the intracoronary bolus administration of eptifibatide during PCI in patients with acute coronary syndromes resulted in higher local platelet glycoprotein IIb/IIIa receptor occupancy, which was associated with improved micro-vascular perfusion demonstrated by an improved Corrected TIMI Frame Count. [27]

The Randomized Leipzig Immediate Percutaneous Coronary Intervention Abciximab IV Versus IC in ST-Elevation Myocardial Infarction Trial showed that intracoronary bolus administration of abciximab in primary PCI is superior to standard intravenous treatment with respect to infarct perfusion (according to ST-segment resolution at 90 minutes). In this study, each group contained 77 patients. [28]

In the RELAX-AMI Trial, the angiographic perfusion grade after PCI was similar between the intravenous abciximab group and previously published results, whereas the intracoronary abciximab group had nonstatistically significant higher perfusion grades. [29]

A retrospective analysis of angiographic and clinical outcomes among 59 patients who received intracoronary eptifibatide as part of clinical management of primary PCI for STEMI between January 2001 and March 2005 showed intracoronary eptifibatide can be administered safely during primary PCI and is associated with few adverse events. [14]

Intracoronary bolus application of tirofiban was not associated with reduction in MACE rates, and enzymatic infarct size compared to intravenous administration in patients with STEMI who underwent primary PCI. At six months the incidence of MACE was 6.25% in IV group and 11.1% in IC group (p=0.45). Peak creatine phosphokinase (CPK) levels between IV and IC groups were also statistically non significant (2657±2181 U/L in IV group and 2529±1929 U/L in IC group) (p=0.92). [30]

For the AIDA STEMI trial, 2065 STEMI patients undergoing PCI, from July 2008 to April 2011, were randomized to receive abciximab by an IV infusion or directly into the blocked coronary artery for 12 hours. Intracoronary bolus administration of abciximab does not add a benefit in comparison to the standard IV bolus, with respect to the combined primary study endpoint consisting of death, reinfarction or new congestive HF within 90 days. Although previous research suggested intracoronary dose during PCI could boost concentration of abciximab at the treatment site, limit heart tissue destruction and improve blood flow, the AIDA STEMI researchers did not find a difference in blood flow or infarct size (assessed by AUC CK-Release, P=0.74), early ST resolution (P=0.37) between the two routes. The IC route might be only related to reduce rates of new congestive heart failure. [31]

As seen, the results of the comparison between intracoronary and intravenous GP IIa/IIIb inhibitor administration during primary PCI in STEMI patients, diffusely vary in many studies and trials. This is, might be, the reason that the AHA and the ACC in the updated 2011 guidelines for PCI, noted that in pateint undergoing primary PCI with abciximab, it may be reasonable to administer intracoronary abciximab (class IIb). But it is not emphasized for other GP inhibitor drugs. [32]

Although in our study, all angiographic, and ECG measurements were blinded, interventionalists were aware of the group assignment. Thus, a potential investigator bias cannot be ruled out entirely. Another important problem was the inadequate number of patient in each group, which was due to wide range of exclusion criteria.

Confirmation of the results with respect to clarification of the long-term effects on infarct size, myocardial reperfusion, ventricular size and function and, more important, on clinical outcome requires a larger trial.

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