Original Article

Platelet GP IIb/IIIa Receptor Inhibition by Eptifibatide in non ST-elevation MI-Acute Coronary Syndrome

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Background: Recent trials of platelet glycoprotein IIb/IIIa receptor inhibitors have improved our understanding to best use these powerful antiplatelet drugs in acute coronary syndrome. We tested the hypothesis that inhibition of GPIIb/IIIa platelet receptor with Eptifibatide is effective as an empiric therapy in patients with acute coronary syndrome who do not necessarily undergo immediate revascularization.
Methods: Since Feb 2006 one hundred and ninety-six patients who had presented with non ST-elevation acute coronary syndrome (NSTE-ACS) were randomly assigned to receive Eptifibatide in addition to standard therapy, for up to 72 hours or routine standard therapy. The primary end point was composite of death and non-fatal myocardial infarction (MI) or urgent target vessel revascularization (TVR) in 30 days.
Results: The incidence of composite end point of death, non fatal MI and urgent TVR was significantly lower in Eptifibatide group than standard group (16% vs. 0% - P value <0.01),particularly in troponin positive subgroup of patients (27.8% vs. 0% - P value <0.01).
Any major adverse reaction such as major bleeding, stroke, or thrombocytopenia was not seen.
Conclusion: Early administration of GP IIb/IIIa receptor inhibitor is recommended in patients with high-risk acute coronary syndrome.

Key words: GP IIb/IIIa Receptor Inhibitor, Eptifibatide, Acute Coronary Syndrome.

Introduction

Disruption of atherosclerotic plaque, leading to platelet aggregation within fibrin mesh[1] and thrombus formation results in acute coronary syndrome, including non ST-segment elevation MI (NSTE MI) and unstable angina. Aggregation of platelet is the pathophysiologic basis of the acute coronary syndrome.[2]

Eptifibatide, a synthetic cyclic heptapeptide, is a selective high affinity inhibitor of the platelet glycoprotein IIb/IIIa receptor[3-5] which is final common pathway of platelet aggregation.

It is recommend in 2007 guidelines of the American College of Cardiology and the American Heart Association, that patients with high-risk features receive aspirin and either clopidogrel or a glycoprotein IIb/IIIa inhibitor before angiography.[6] The European Society of Cardiology favors early dual antiplatelet therapy with aspirin and clopidogrel, with the addition of a glycoprotein IIb/IIIa inhibitor reserved for patients with an elevated troponin level, ST-segment depression, or diabetes.[7] Administration of platelet glycoprotein IIb/IIIa antagonists are also reported to decrease complications following percutaneous coronary intervention (PCI).[8]

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Several randomized controlled trials, have assessed the therapeutic effect of Eptifibatide, but there is not enough studies to prove their effectiveness and more investigations are needed to be conclusive.

In regard to inadequate studies performed in Iran the present study was designed to assess the hypothesis that inhibition of platelet aggregation with Eptifibatide would have an incremental benefit beyond that of heparin and aspirin in reducing the frequency of adverse outcomes in patients with acute coronary syndrome, NSTEMI.

Patients and Methods

The present study was performed since Feb 2006, and comprised one hundred and ninety-six Patients, with symptoms of ischemic chest pain at rest, lasting more than 10 minutes, within the previous 24 hours. They either had electrocardiographic changes indicative of ischemia (new ST-segment depression of more than 0.5 mm, T-wave inversion of more than 1 mm) and/or high serum concentration of myocardial isoenzyme (CKMB or Cardiac Troponin).[9] Criteria for exclusion included persistent ST-Segment elevation of more than 1 mm , active bleeding or a history of bleeding diathesis , gastrointestinal or genitourinary bleeding within 30 days before enrollment, systolic blood pressure above 200 mmHg and/or diastolic blood pressure above 110 mmHg, a history of major surgery within the previous 6 weeks, a history of non-hemorrhagic stroke within the previous 30 days or any history of hemorrhagic stroke, renal failure, pregnancy, and age above 70 years.

Patient received Eptifibatide at a bolus dose of 180 µg/kg followed by an Eptifibatide infusion of 2 µg/kg/min[10] in addition to standard therapy for up to 72h or routine standard therapy. Cardiac catheterization was performed during this period. All patients received Aspirin (160 mg/day) and heparin and Plavix. Intravenous heparin was given as a bolus does of 5000 unit, followed by an infusion of 1000 units/hour, with activated partial thromboplastin time maintained within the range of 50 to 70 seconds. Platelet count was carried out at base line with daily monitoring during the drug infusion. Drug infusion was discontinued if platelet count was less than 100000 per/mm^3. The primary end point was a composite of death or nonfatal MI and urgent TVR in 30 days.

Statistical analysis

Continuous variables were compared using the student's t-test for unpaired samples. Differences between proportions were compared using the Chi-square test. SPSS 11.5 software package was used for the statistical analysis and a P value < 0.05 was considered statistically significant.

Ethical consideration

Explaining our goals, each patient was asked to participate in our study. Informed consent was obtained from all patients who could interrupt their cooperation whenever desired.

Results

A total of 196 patients were randomly assigned to the study groups during one year, 98 patients to the high dose Eptifibatide group and 98 to the standard therapy group.

Patients were enrolled with a median of 14

Table 1. Baseline Characteristics according to study group *

Characteristics	Eptifibatide n=98	Standard n=98
Age (yr) Range	50.9 (37- 69)	54.8 (36- 69)
Female Sex (%)	35.7	50
Hypertension (%)	38.1	42
Diabetes mellitus (%)	33.3	38
Hypercholesterolemia (%)	52.4	59
Family history of CAD (%)	21.4	20
CK-MB or TnI rise (%)	47.5	42
Ejection Fraction (mean)	47.8	46.5
ST-segment depression%	76.2	76.6
T-Wave inversion%	61.9	57.5
S.V.D %	48	62
2.V.D %	17	16
3.V.D %	35	22

* None of the differences between two groups are statistically significant.

hours after the onset of symptoms. The baseline characteristics of the patients are shown in Table 1.

Revascularization was done slightly more frequently in patients receiving Eptifibatide than in the standard group (76% vs. 66%).

Treatment with Eptifibatide was associated with a significant reduction in the incidence of composite end-point of death or myocardial infarction and urgent target vessel revascularization in 30 days.

Incidence of composite end-point in 30 days follow up was 16% and 0% in the standard and Eptifibatide groups respectively (P <0.01) (Fig. 1).

In subgroup of troponin positive patients, the rate of myocardial infarction was 27.8% in standard versus 0% in Eptifibatide group (P <0.01). In patients with ST-segment depression, the respective rates of MI were 10.5% in standard and 0% in Eptifibatide group.

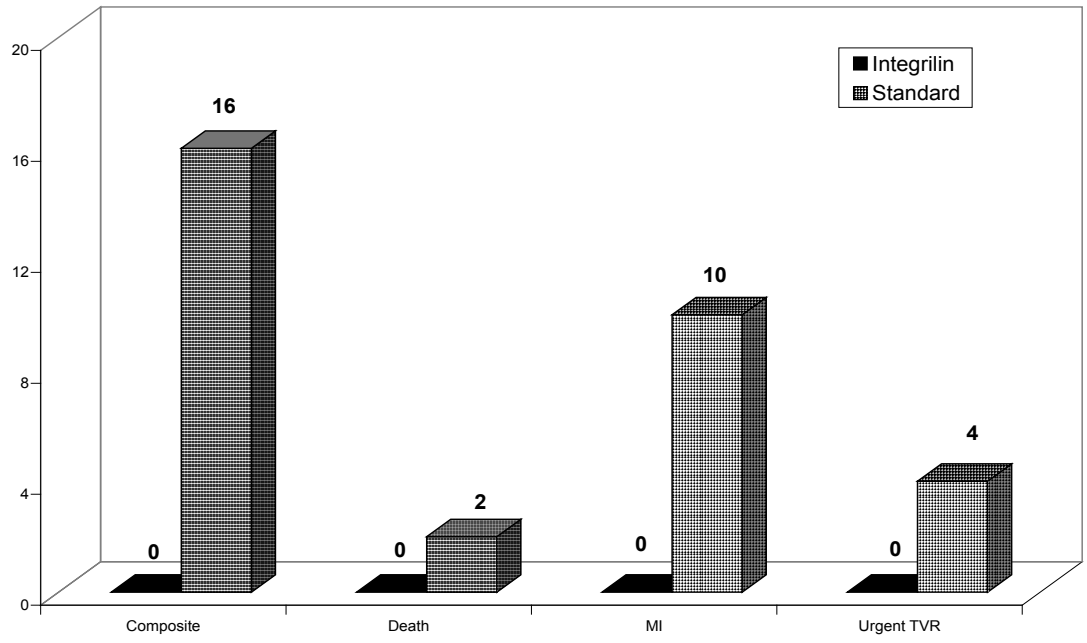

Figure 1. Incidence of the components of the composite end-point in study groups

Minor bleeding including epistaxis or gingival bleeding was more common among Eptifibatide group compared with standard group (7% vs. 0%). There was no major Bleeding among either group.

Discussion

The hypothesis that Eptifibatide, a selective high-affinity inhibitor of the platelet glycoprotein IIb/IIIa receptor, would have an incremental benefit beyond that of heparin and aspirin in reducing the frequency of adverse outcome in patients with NSTE ACS, have been demonstrated in large randomized clinical trials.[10-16]

However, the magnitude of benefit in various data has consistently favored glycoprotein IIb/IIIa receptor inhibition over placebo. There has been a consistent reduction in the incidence of death and myocardial infarction and the need for revascularization in patients with NSTE ACS.[11,17,18]

Our study has shown that Eptifibatide reduces the incidence of death or nonfatal myocardial infarction and urgent TVR. The absolute 16% reduction of composite end-point was achieved during drug infusion and persisted for 30 days. The high incidence of the composite end-point reduction in our study may have reflected our selection of patients with more severe disease as well as our rigorous search for electrocardiographic and laboratory data to establish and verify infarction or reinfarction. The distribution of cardiovascular risk factors was similar to the distributions in other large studies of the same patients.[19,20]

The use of Eptifibatide was not associated with increased major bleeding, stroke, or thrombocytopenia. The beneficial effect of Eptifibatide was the same in males and females.

Subgroup studies using baseline troponin or CK-MB have found that the benefit of GP IIb/IIIa inhibitor appears to be greatest in high risk patients.[21-23]

In our study greater benefit of Eptifibatide was also seen in those with positive troponin I. The primary end-point of MI was 27.8% in standard group compared to 0% in Eptifibatide treated patients ($P<0.01$).

In addition this study showed that the rate of myocardial infarction was significantly lower in patients of Eptifibatide group with ST segment depression ($P <0.05$). Patients with ST-segment depression have two to three-fold greater absolute benefits than those without ST-changes.[16,22,23]

Among patients with moderate to high risk ACS undergoing an invasive treatment strategy, deferring the routine upstream use of GPIIb/IIIa inhibitors for selective administration in the cardiac catheterization laboratory, only those subjected to percutaneous coronary intervention showed a numerical increase in composite ischemia that, while not statistically significant, did not meet the criterion for no inferiority.[24,25]

These results support the hypothesis that blocking the GP IIb/IIIa receptors is useful when the receptors are activated, but less so when they are not.[21]

In conclusion, according to current evidence, early administration of GP IIb/IIIa receptor inhibitor is recommended in patients with high-risk acute coronary syndrome.

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References

1 Chesebro JH, Fuster V. Thrombosis in unstable angina. *N Engle J Med* 1992;**327**:192-4. [1608410]
2 Braunwald E. Unstable angina: an etiologic approach to management. *Circulation* 1998;**98**:2219-22. [9826306]
3 Philips DR, Scarbrough RM. Clinical pharmacology of Eptifibatide. *Am J Cardiol* 1997;**80**:11B-20B. [9291241]
4 Denis MS,Henzel WJ, Pitti RM ,et al. Platelet glycoprotein IIb/IIIa Protein antagonists from snake venoms: evidence for a family of platelet –aggregation inhibitors. *Proc Natl Acad Sci U S A* 1990;**87**:2471-75. [2320569]
5 scarborough RM , Naughton MA, Teng W, et al. Design of potent and specific integrin antagonists . Peptide antagonist with high specificity for glycoprotein IIb/IIIa. *J Biol Chem* 1993;**268**:1066-73. [8419315]
6 Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol* 2007;**50**:e1-e157. [17692738]
7 Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007**;28**:1598-660. [17569677]
8 ESPRIT Investigators. Novel dosing regimen of Eptifibatide in planned coronary stent implantation (ESPRIT): a randomized, placebo-controlled trial. *Lancet* 2000;**356**:2037-44. [11145489]
9 Harrington RA. Design and methodology of the PURSUIT trial: evaluating Eptifibatide for acute ischemic coronary syndromes. *Am J cardiol* 1997;**80**:34B-38B. [9291244]
10 Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998;**339**:436-43. [9705684]
11 The platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by unstable Signs and Symptoms (PRISM-PLUS) Trial Investigators: Inhibition of the Platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable Angina and non-Q-Wave myocardial infarction. *N Engl J Med* 1998;**338**:1488-97. [9599103]
12 Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA* 2006;**295**:1531-8. [16533938]
13 Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. *Lance*t 1997;**349**:1422-8. [164315]
14 Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet* 1997;**349**:1429-35. [9164316]
15 Tricoci P, Newby LK, Kandzari DE, et al. Present and evolving role of Eptifibatide in the treatment of acute coronary syndromes*. Expert Rev Cardiovasc Ther* 2007;**5**:401-12. [17489665]
16 Curran MP, Keating GM. Eptifibatide: a review of its use in patients with acute coronary syndromes and/or undergoing percutaneous coronary intervention. *Drugs* 2005;**65**:2009-35. [16162023]
17 The platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Eng J Med* 1998;**338**:1498-505. [9599104]
18 International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. The PARAGON Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. Circulation 1998;97:2386-95. [9641689]
19 A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb investigators. *N Engl J Med* 1996;**335**:775-82. [8778585]
20 Plosker GL, Ibbotson T. Eptifibatide: a pharmacoeconomic review of its use in percutaneous coronary intervention and acute coronary syndromes. *Pharmacoeconomics* 2003;**21**:885-912. [12908844]
21 Théroux P, Labarthe B. Coping with new challenges in acute coronary syndromes. *Can J Cardiol* 2006;**22**:13c-20c. [16929386]
22 Demirkan B, Guray Y, Guray U, Korkmaz S. Differential diagnosis and management of acute profound thrombocytopenia by tirofiban: a case report. *J Thromb Thrombolysis* 2006;**22**:77-8. [16786237]
23 Cannon CP. Small molecule glycoprotein IIb/IIIa receptor inhibitors as upstream therapy in acute coronary syndromes: Insights from the TACTICS TIMI-18 trial. *J Am Coll Cardiol* 2003;**41**:43s-48s. [12644340]
24 Stone GW, Bertrand ME, Moses JW, et al. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY Timing trial. **JAMA** 2007;**297**:591-602. [17299194]
25 Mahaffey KW, Harrington RA. Optimal timing for use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: questions, answers, and more questions**. JAMA** 2007;**297**:636-9. [17299199]