Comparison of intracoronary versus intravenous administration of tirofiban in primary percutaneous coronary intervention

Primer perkütan koroner girişim uygulanan hastalarda tirofibanın intrakoroner ve intravenöz bolus dozlarının karşılaştırılması

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ABSTRACT

Objective: The purpose of this study was to compare the intravenous bolus dose of tirofiban with intracoronary bolus dose in primary percutaneous coronary intervention (PCI) with regard to in hospital and six months clinical outcomes and peak cardiac enzyme levels.
Methods: We retrospectively examined 84 ST elevation myocardial infarction (STEMI) patients who underwent primary PCI from March 2006 to February 2007. All patients received the systemic bolus dose of tirofiban 10 mcg/kg either via intracoronary (IC) or intravenous (IV) route, followed by a 36 hours of IV infusion at 0.15 mcg/kg/min. Thirty six patients in IC group were compared with 48 patients in IV group in terms of peak cardiac enzyme levels, in-hospital and six months major adverse cardiac events (MACE) rates (death, myocardial infarction and repeat revascularization). Fisher's exact test, Yates Chi-square, unpaired Student's t-test and Mann-Whitney U test were used for statistical analysis.
Results: There was no difference in cardiovascular risk profile or cardiac history between two groups. At six months the incidence of MACE was 6.25% in IV group and 11.1% in IC group (p=0.45). Peak cardiac 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).
Conclusion: Intracoronary bolus application of tirofiban was not associated with reduction in MACE rates compared to intravenous administration in patients with STEMI who underwent primary PCI. Future prospective trials with higher bolus doses of IC tirofiban should addressed to clarify this issue. *(Anadolu Kardiyol Derg 2010; 10: 40-5)*
Key words: Myocardial infarction, glycoprotein IIb/IIIa inhibitors, coronary stenting

ÖZET

Amaç: Bu çalışmadaki amacımız primer perkütan koroner girişim (PKG) uygulanan ST elevasyonlu miyokart enfarktüsü hastalarında bir glikoprotein IIb/IIIa reseptör blokeri olan tirofibanın intrakoroner (İK) ve intravenöz (İV) bolus dozlarının klinik sonuçlar ve zirve kardiyak enzim seviyeleri açısından karşılaştırılmaktır.
Yöntemler: Merkezimizde Mart 2006 ve Şubat 2007 tarihleri arasında primer PKG uygulanan 84 hasta retrospektif olarak incelendi. Hastalara 10 mcg/kg tirofiban bolus dozu İK veya İV yolla uygulandı ve 36 saat boyunca 0.15 mcg/kg/dk dozundan IV yolla devam edildi. İK gruptaki 36 hasta ve IV gruptaki 48 hasta zirve kardiyak enzim seviyeleri, hastane içindeki ve 6. aydaki majör istenmeyen kardiyak olay (ölüm, miyokardiyal enfarktüs, tekrarlayan revaskülarizasyon) oranları açısından karşılaştırıldı. İstatistiksel değerlendirmede Fisher's test, Yates Ki-kare, eşleştirilmemiş Student t testi ve Mann-Whitney U testi kullanıldı.
Bulgular: Kardiyovasküler risk profilleri ya da geçirilmiş kardiyak olaylar açısından iki grup arasında fark yoktu. Altı aylık takipte majör istenmeyen kardiyak olay oranları İV grupta %6.25 ve İK grupta ise %11.1 olarak saptandı (p=0.45). Her iki grupta zirve kardiyak fosfokinaz seviyeleri arasında istatistiksel bir fark saptanmadı (İV grupta 2657±2181 U/L ve İK grupta 2529±1929 U/L) (p=0.92).
Sonuç: Primer PKG uygulanan ST elevasyonlu miyokart enfarktüsü hastalarında tirofiban bolus dozunun intrakoroner uygulanması majör istenmeyen kardiyak olay sıklığını intravenöz uygulamaya göre azaltmamıştır. İleride yapılacak ve daha yüksek intrakoroner bolus dozunun kullanıldığı prospektif çalışmalar bu konunun açıklanmasına ışık tutacaktır. *(Anadolu Kardiyol Derg 2010; 10: 40-5)*
Anahtar kelimeler: Miyokart enfarktüsü, glikoprotein IIb/IIIa reseptör blokerleri, koroner stentleme

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Introduction

Timely performed primary percutaneous coronary intervention (PCI) is currently the preferred treatment in ST elevation myocardial infarction (STEMI) and it is superior to fibrinolytic therapy in terms of patient survival rates (1, 2). It has been showed that glycoprotein (GP) IIb/IIIa receptor blockers improve angiographic results and clinical outcomes of STEMI patients when used as an adjunctive treatment to PCI (3). Recent studies with abciximab, which is a commonly used GP IIb/IIIa antagonist, have showed that intracoronary (IC) bolus dose is more effective than IV bolus dose in reducing major adverse cardiac events (MACE) in STEMI (4). The IC bolus administration provides high concentrations of drug during first pass at the culprit lesion and in the distal bed of the culprit coronary vessel, facilitating the effects of the drug (5). Tirofiban is another GP IIb/IIIa antagonist and it is usually administered as an intravenous (IV) bolus injection followed by a maintenance infusion of 18-36 hours in STEMI patients (6, 7). However, there is only one clinical trial in which the efficacy of IC administration of tirofiban was investigated in acute coronary syndrome (ACS) patients (8).

In this retrospective trial, we studied whether intracoronary bolus administration of tirofiban is associated with a reduced clinical event rate and less cardiac enzyme release compared to the intravenous bolus injection in primary PCI patients.

Methods

Patient selection

We examined 84 consecutive STEMI patients who underwent primary PCI from March 2006 to February 2007. Patients who received coronary stent implantation and tirofiban were included in the study. They were retrospectively stratified according to the method of application of tirofiban.

Tirofiban administration protocol

All patients received the systemic bolus dose of tirofiban 10 mcg/kg either via IC or IV route, followed by a 36 hours of IV infusion at 0.15 mcg/kg/min. In both groups bolus tirofiban injection was administered after the completion of coronary angiography, but immediately before angioplasty of infarct-related artery. There were three operators and the route of administration of tirofiban was based on operator's discretion. The intracoronary bolus administration was given at five minutes via the guiding catheter. Flow in the PCI-targeted vessel was assessed before and after the procedure by Thrombolysis in Myocardial Infarction (TIMI) flow grade (9). All patients received standard pharmacological therapy, including unfractionated heparin, aspirin and clopidogrel. Heparin bolus dose was 70IU/kg and clopidogrel loading dose was 600 mg. Clopidogrel was followed by 75 mg/day for at least 12 months.

Cardiac Enzyme Measurement

Blood was drawn for creatine kinase (CK) and CK-MB at baseline, 6, 12 and 24 hours after the procedure.

Left Ventricular Ejection Fraction Measurement

Left ventricular ejection fraction was assessed by standard 2-dimensional echocardiography with modified Simpson method.

Major Adverse Cardiac Events (MACE)

MACE was defined as acute myocardial infarction (STEMI and non-ST elevation myocardial infarction), repeat revascularization or death which occurred during hospital period or within 6 months after primary PCI.

Statistical Analysis

Continuous variables were presented as mean±1 SD. Unpaired Student's t-test or Mann-Whitney U-test was performed for group comparison with continuous, nonparametric or parametric variables. Yates chi-square or Fisher's exact test was used to compare the IC and IV groups on qualitative variables (comparison of two proportions). All statistical analyses were performed using Instat (Instat V3.05 2000, Graphpad Software, San Diego, CA). For all analyses, a two-tailed $p<0.05$ was considered statistically significant.

Results

The mean age was 56±10 years in IV tirofiban group (IV group) and 55±12 years in IC tirofiban group (IC group) (p=0.96). There was no difference between two groups in cardiovascular risk profile, cardiac history and TIMI flow grade before and after PCI (Table 1).

In hospital MACE rates were 2.7% in IC group and 2.1% in IV group (p=1.00). Total MACE rates in the IV group at six months was 6.25% vs. 11.1 % in IC group (p=0.45) (Table 2). The individual components of MACE in patients with IV versus IC group were as follows: death - 2.1% vs. 2.7%; repeat revascularization - 4.1% vs. 8.3%; recurrent myocardial infarction 4.1% vs. 8.3% (Table 2).

Peak CPK levels and CPK- MB levels did not differ between groups (p=0.92 and p=0.51, respectively) (Table 3). In subgroup analysis, anterior MI patients in IV group had higher peak CPK (3444± 2600 U/L vs 2342±2078 U/L) and CPK-MB (451±360 U/L vs 304±328 U/L) levels than IC group, but the differences were not statistically significant (p=0.10 and p=0.15, respectively).

Echocardiographic analysis was performed in 15 of 36 patients in IC group and 36 of 48 patients in IV group. There was a trend toward higher ejection fraction in IC group than in IV group (50±7% vs 45±6%), but it did not reach statistical significance (p=0.06).

Discussion

Our study of patients undergoing primary PCI for treatment of STEMI did not show any benefit of intracoronary bolus appli-

Table 1. Patient and procedural characteristics

Variables	IC Tirofiban (n=36)	IV Tirofiban (n=48)	p*
Age, year	55±12	56±11	0.96
Cardiovascular risk factors			
Male sex, n (%)	33 (91)	43 (90)	0.74
Family history, n (%)	12 (33)	14(29)	0.86
Hyperlipidemia, n (%)	24 (67)	38 (79)	0.29
Hypertension, n (%)	10 (28)	20 (42)	0.27
Diabetes mellitus, n (%)	5 (14)	12 (25)	0.32
Cigarette smoking, n (%)	31 (86)	42 (87)	0.85
Cardiac history			
Previous myocardial infarction, n (%)	3 (8)	4 (8)	1.00
Previous coronary artery bypass graft surgery, n (%)	1 (3)	1 (2)	1.00
Localization of MI			
Anterior, n (%)	23 (64)	23 (49)	0.21
Inferior, n (%)	13 (36)	25 (51)	0.92
Target Vessel			
Left anterior descending, n (%)	23 (64)	27 (56)	0.63
Right coronary artery, n (%)	13 (36)	16 (33)	0.97
Circumflex artery, n (%)	1 (3)	5 (10)	0.23
Thrombus in culprit vessel	23 (64)	31 (67)	0.94
TIMI flow			
Before PCI (Grade 0-1), n (%)	27 (75)	39 (81)	0.67
After PCI (Grade 3), n (%)	30 (83)	39 (81)	0.80

Categorical variables are expressed as numbers (percentages) and continuous variables as mean± standard deviation
* Unpaired Student's t, Mann-Whitney U , Chi-square and Fisher's exact tests
IC - intracoronary, IV - intravenous, MI - myocardial infarction, PCI - percutaneous coronary intervention,
TIMI - thrombolysis in myocardial infarction

cation of tirofiban in terms of end- points compared with the standard intravenous bolus dose of tirofiban, both followed by 36-hour infusion.

The benefits of platelet GP IIb/IIIa receptor inhibitors have been proved in a variety of clinical situations, including elective stenting and non–ST-elevation acute coronary syndromes (10-12). Recent studies have also shown clinical improvement with abciximab in the setting of STEMI and primary PCI (13, 14). Although the effects of tirofiban in STEMI has not been well established, there were published trials which investigated the role of tirofiban in STEMI and primary PCI. In TIGER-PA pilot trial (7) early administration of intravenous tirofiban improved angiographic outcomes and was safe in patients undergoing primary PCI. Valgimigli et al. (15) investigated the effect of intravenous tirofiban (25 µg/kg bolus dose) and sirolimus- eluting stents as compared with abciximab infusion and bare metal stent implantation in patients with STEMI undergoing primary PCI (15). Tirofiban therapy was shown non-inferior to abciximab therapy in prespecified end-points and also caused less thrombocytopenia than abciximab therapy.

Very recently published FATA (Facilitated angioplasty with tirofiban or abciximab) trial enrolled 692 patients with STEMI (16). Patients were randomized to receive tirofiban (25 µg/kg bolus dose) (n=341) or abciximab (n=351). Results of this study showed a slight improvement in ST segment resolution with abciximab therapy but it did not translate into clinical end-points which were similar between 2 groups of patients on 30th day of follow up (16). Post hoc analysis of FATA trial also failed to demonstrate any benefit of abciximab over tirofiban therapy in left ventricular function recovery after primary PCI (17).

Finally, Luca et al. (18) published a meta-analysis of six randomized controlled study comparing abciximab with small molecule GP IIb/IIIa receptor inhibitors (tirofiban and eptifibatide) in primary PCI patients. This meta-analysis showed similar results between abciximab and small molecules in terms of angiographic, electrocardiographic and clinical outcomes (18).

Although IV application is widely used, IC administration of GP IIb/IIIa inhibitors in PCI is a relatively new issue. The rationale for the use of the drug through the intracoronary route relates to two reasons. First because of dose response relation-

Table 2. Clinical outcomes at 6th month

Variables	IC Tirofiban (n=36)	IV Tirofiban (n=48)	p*
MACE, n (%)	4 (11.1)	3 (6.25)	0.45
Death, n (%)	1 (2.7)	1 (2.1)	1.00
Myocardial infarction, n(%)	3 (8.3)	2 (4.1)	0.64
Repeat revascularization, n(%)	3 (8.3)	2 (4.1)	0.64

Categorical variables are expressed as numbers (percentages)
* Chi-square test
IC - intracoronary, IV - intravenous, MACE - major adverse cardiac events

Table 3. Cardiac enzymes and left ventricular function

Variables	IC Tirofiban (n=36)	IV Tirofiban (n=48)	p
Peak CPK, U/L	2529±1929	2657±2181	0.92
Peak CPK-MB, U/L	311±274	354±308	0.51
LVEF**, %	50±7	45±6	0.06

Continuous variables expressed as mean±1 standard deviation
* Unpaired Student's t and Mann-Whitney U tests
CPK - creatinine phosphokinase, IC - intracoronary, IV - intravenous, LVEF - left ventricular ejection fraction
** Echocardiographic examination was performed in 15 of 36 patients in IC tirofiban group and 36 of 48 patients in IV tirofiban group

ship, increasing the concentration of drug at the coronary thrombosis site facilitates the resorption of thrombus and prevents microcirculatory dysfunction. Second, when distal coronary flow is severely compromised, intravenous administration of drug may not reach the thrombus rich culprit lesion and limits beneficial effects of drug (19). Almost all IC applications of GP IIb/IIIa inhibitor studies were conducted with abciximab so far. Wöhrle et al. (4) have shown that IC bolus application of abciximab was associated with a reduction of MACE compared with IV bolus application (10.2% versus 20.2%) (p<0.0008) in 403 acute coronary syndrome patients. Bellandi et al. (20) concluded that IC abciximab was associated with a greater degree of myocardial salvage and substantial reduction in infarct size than IV bolus in primary PCI patients with a statistically significant difference in peak CPK levels between treatment groups. More recently in a prospective study of 633 STEMI patients who received IC bolus dose of abciximab, the incidence of MACE has been shown to be 3.6% at 30 days and it was lower compared to previous studies (21).

The first reported use of IC tirofiban in the thrombus containing coronary artery lesion with no-reflow phenomenon was performed by Yang et al. (22). They expressed that coronary flow was immediately restored following the administration of IC tirofiban.

Very recently, Wu et al. (8) published a prospective study, which compared IC bolus dose of tirofiban with IV bolus dose in 118 ACS patients (8). The average age of these patients, was 75±2 years and 60% of them had been diagnosed as STEMI. Compared with the IV bolus group IC bolus group showed better TIMI flow grades and TIMI myocardial perfusion grades immediately after PCI. The 14- day composite major cardiac events rate was lower in IC group but was similar between two groups at 30-day follow up (7% vs. 1.7%, p=0.350). The left ventricular ejection fraction in the IC group was higher than in IV group on 30th day following PCI (p=0.003). However, in this study investigators did not perform subgroup analysis so these results could not solely be attributable to STEMI patients.

Our study is the first study, which compare IC bolus dose of tirofiban with IV bolus dose in primary PCI patients only.

Previous trials proved that the level of peak cardiac enzymes are directly associated with myocardial infarct size and are also independent predictors of mortality (23, 24). Our study did not show statistically significant difference in terms of MACE rates and peak cardiac enzyme levels between IV and IC tirofiban groups. There might be two possible explanations of these results. First, our study patients represented younger and lower risk population. The average age of patients was only 55 years in our study whereas it was 75 years in the study of Wu et al. (8). The second reason may be related with bolus dose of tirofiban, which is 10 µg/kg in our study. Subsequent dose ranging studies showed that increasing the tirofiban bolus dose from 10 to 25 µg/kg provided an optimal level of platelet inhibition and might even lead to a more consistent platelet inhibition than abciximab (25, 26). Ernst et al. (27) evaluated the extent of platelet aggregation inhibition in patients with STEMI undergoing primary PCI with clopidogrel, abciximab, standard bolus dose of tirofiban (10 µg/kg) and high bolus dose of tirofiban (25 µg/kg). This study showed that only with the high bolus dose tirofiban regimen, the mean periprocedural level of platelet aggregation inhibition exceeds 80%. Therefore, prospective trials should be designed to delineate the effect of high dose tirofiban therapy in STEMI patients treated with primary PCI.

Study limitations

A retrospective, nonrandomized study design and small sample size are the major limitations of the study. Another limiting factor was lack of multivariable statistical analysis.

Conclusion

In patients with STEMI undergoing primary PCI, intracoronary bolus application of tirofiban was not associated with reduction in MACE rates compared to intravenous application. Future prospective trials with higher bolus doses of IC tirofiban are indicated to clarify this issue.

Conflict of interest: None declared.

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