Long term tirofiban infusion before percutaneous coronary intervention in patients with angiographically massive intracoronary thrombus

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ABSTRACT

الأهداف: من أجل تقييم أثر التسريب بعقار تيروفيبان على المدى الطويل قبل التدخل التاجي عبر الجلد على ضوء نتائج تصوير الأوعية لوجود الجلطة التي يمكن رؤيتها داخل التاجي ومقارنة ذلك مع الطريقة التقليدية بدون التسريب.

الطريقة: من بين ٢٨٣٥ حالة أجريت في مستشفى غازي الجامعي في الفترة ما بين عام ١٩٩٩م وعام ٢٠٠٦م،شملت الدراسة ١٥٦ (٥٫٥٪) مريضاً يعاني من وجود كتلة متجلطة وأجريت لهم عملية التدخل التاجي عبر الجلد. من بين هؤلاء المرضى والبالغ عددهم ١٥٦ كان هنالك ٨٢ مريضاً (٥٣٪) أجريت لهم طريقة التدخل التاجي عبر الجلد على ضوء إظهار التجلط بواسطة تصوير الأوعية بدون تسريب عقار تيروفيبان وسميت مجموعتهم بالمجموعة أ. ولكن تلقى ٧٤ مريضاً (٤٧٪) التسريب على المدى الطويل بعقار تيروفيبان قبل إجراء التدخل التاجي عبر الجلد وسميت مجموعتهم بالمجموعة ب.

النتائج: على الرغم من عدم وجود فرق في الخط القاعدي للتجلط في احتشاء عضلة القلب بين المجموعتين الى أن ذلك أقل بشكل ملحوظ في المجموعة ب مقارنة مع المجموعة أ بعد التدخل التاجي عبر الجلد (٨٫١٪ مقابل ٢٣٫٢٪، نسبة الخطأ= ٠٫٠١٥). كما كان انخفاض حمل التجلط في المجموعة ب بعد التسريب بعقار تيروفيبان ذو دلالة إحصائية أيضاً مقارنة مع المستويات قبل التسريب بعقار تيروفيبان (١٫٧٧+١٫٠٥ مقابل ٣٫٤٢+ ٠٫٧٦ على التوالي، نسبة الخطأ أصغر من ٠٫٠٠١). لدى المجموعة ب مميزات تيار أفضل مع ٩١٫٩٪ بعد التدخل التاجي عبر الجلد. كان التدخل ناجحاً في التقنية العظمى ولكن تم ملاحظة عدم الانحسار في ١٧ مريضاً (٢٠٫٧٪) في المجموعة أو مريضين (٢٫٧٪) في المجموعة ب (نسبة الخطأ أصغر من ٠٫٠٠١) تمت ملاحظة نزيف كبير تطلب عملية نقل للدم في كلتا المجموعتين (٣ مرضى في المجموعة أ) و(مريضين في المجموعة ب) نتيجة الى نزيف معدي معوي او وجود أورام دموية في موقع المدخل (٣٫٧٪ مقابل ٥٫٤٪).

خاتمة: تبدو إستراتيجية طريقة التسريب بعقار تيروفيبان قبل التدخل التاجي عبر الجلد في التجلط الذي يحتوي على آفات طريقة آمنة ويمكن رؤيتها في تجنب (عدم الإنحسار) وإذابة الكتلة المتجلطة.

Objective: To evaluate the impact of long term tirofiban infusion before percutaneous coronary intervention (PCI) on the angiographic results in the setting of visible intracoronary thrombus and compare this with conventional PCI performed without tirofiban.

Methods: Out of 2835 PCI procedures performed in Gazi University Hospital, Ankara, Turkey between 1999 and 2006, 156 (5.5%) patients with massive thrombus in whom PCI were applied, were included in this retrospective study. Out of these 156 patients, 82 (53%) had PCI in the presence of angiographically apparent thrombus without tirofiban and named as group A. The remaining 74 (47%) received long term tirofiban infusion before PCI and were named as group B.

Results: Although the baseline thrombolysis in myocardial infarction (TIMI) 0-2 flow was no different between the groups, it is significantly lower in group B compared to group A after the PCI (8.1% versus 23.2%, p=0.015). The decrease in thrombus burden in group B after tirofiban infusion was also statistically significant compared to pre-tirofiban levels (1.77±1.05 versus 3.42±0.76, p<0.001). Group B had better flow characteristics with a 91.9% TIMI 3 flow after PCI. Intervention was successful in the majority technically, however, no reflow was observed in 17 patients (20.7%) in group A and in 2 patients (2.7%) in group B (p<0.001). Major bleeding requiring transfusion was observed in both groups A (3 patients) and B (4 patients) due to gastrointestinal bleeding or access site hematomas (3.7% versus 5.4%, non significant).

Conclusion: Pre-PCI longterm tirofiban infusion strategy in thrombus containing lesions seems to be a safe and feasible approach in avoiding "no re-flow" and dissolving the massive thrombus.

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Intracoronary thrombus, which is usually associated with acute coronary syndromes, can be troublesome especially during percutaneous coronary interventions (PCI). No re-flow, abrupt vessel occlusion, and distal embolization are frequently noted.[1-3] Recently, large trials demonstrated successful results in the setting of acute coronary syndromes associated with intracoronary thrombus by the use of glycoprotein IIb/IIIa (GPIIb/IIIa) receptor blockers as an adjunct to the catheter based therapy.[4] Tirofiban is a highly specific inhibitor of GP IIb/IIIa receptors located on the surface of the platelets. It was shown to be effective during PCI, especially in the setting of acute coronary syndromes.[5,6] Obtaining Thrombolysis In Myocardial Infarction (TIMI) 3 flow with PCI was associated with a better prognosis in acute myocardial infarction (AMI).[7] Brisk TIMI 3 flow immediately after intervention minimizes the ischemic insult on myocardium. The Global Utilization of Streptokinase and Tissue-Type Plasminogen Activator for Occluded Coronary Arteries trial demonstrated a poorer clinical outcome in cases where TIMI 3 flow cannot be obtained.[8] However, PCI related major complications occurred in patients with unstable angina, likely due to the plaque fissuring and thrombus that is frequently present. Abrupt closure (no re-flow) at the angioplasty site occurs in 11-50% of patients who undergo balloon angioplasty in the setting of AMI.[9-11] Primary thrombus propagation may be more important when dilation is performed in the setting of pre-existing thrombus (unstable angina and myocardial infarction).[12] However, long-term tirofiban infusion by overcoming these potential complications may improve blood flow in this thrombogenic milieu. The aim of this study was to evaluate the impact of long-term tirofiban infusion before PCI in the setting of massive visible intracoronary thrombus on the angiographic parameters and compare it with the conventional PCI group.

Methods. ***Study population.*** We reviewed our institutional interventional database from 1999 through December 2006 at Gazi University Hospital, Ankara, Turkey and identified all the patients who had angiographically visible massive intracoronary thrombus. The study protocol was approved by the Local Ethics Committee. The inclusion criterion for the study was the appearance of massive thrombus in any coronary artery. Out of 2835 PCI performed during this period we identified 156 (5.5 %) patients with massive thrombus in whom PCI were applied. Out of these 156 patients, 82 (53%) had PCI in the presence of angiographically apparent thrombus without tirofiban and were named as group A. However, 74 (47%) received long-term tirofiban infusion (35.3±25 hours) before PCI and named as group B. Only the cases with definite, floating, and accumulated thrombus proximal or distal to the lesion and abrupt cut off major arteries were taken into evaluation. Patients who do not have control coronary angiography after tirofiban infusion were excluded from the study.

Angiographic evaluation. The Institutional database was analyzed and angiograms reporting the presence of massive thrombus were gathered. Angiograms were reviewed and graded by 2 independent film readers unaware of the study purpose to assess thrombus burden and TIMI flow grades.[13] Contrast flow through the epicardial artery was graded using the standard TIMI trial flow scale of 0-3. "No re-flow" was defined as an acute impairment of blood flow to TIMI 0-1 after successful dilation. Thrombolysis In Myocardial Infarction 2 flow was defined as "Slow Flow". Angiographic success was defined as TIMI flow grade 3. Slow flow or no re-flow phenomena were treated with intracoronary nitroglycerin (200 µg) followed by intracoronary Verapamil (150-250 µg). We used an angiographic thrombus scoring system based on the size of the thrombus (0 = no thrombus; 1 = intraluminal haziness; 2 = definite thrombus < 1/2 vessel diameter; 3 = definite thrombus 0.5-2 vessel diameters; 4 = definite thrombus > 2 vessel diameters).[14] Quantitative coronary angiography (QCA) was performed with the use of an automatic edge detection system.

Percutaneous coronary interventions procedure. The PCI was deferred if the patient was stable clinically and had definite massive intracoronary thrombus. Tirofiban infusion was started immediately to patients who were eligible, clinically stable, and had no contraindication to tirofiban. Tirofiban was administered at 10 mcg/kg bolus for 3 minutes and then at 0.15 mcg/kg/min in

Table 1 - Clinical characteristics.

Variables	Control group (n=82)	Tirofiban group (n=74)	*P*-value
Age (years)	57.5 ± 11.6*	55.1 ± 10.0*	0.174
Male	72 (87.8)	66 (89.2)	0.787
Diabetes mellitus	12 (14.6)	17 (23.0)	0.593
Hypertension	32 (39.0)	32 (43.2)	0.181
Previous MI	15 (18.3)	15 (20.3)	0.754
Presentation			
NSTEACS,	47 (57.3)	58 (78.4)	0.005
STEMI	35 (42.7)	16 (21.6)	

*mean ± SD, Data are expressed as number and (percentage).
MI - myocardial infarction,
NSTEACS - non ST segment elevation acute coronary syndrome,
STEMI - ST segment elevation myocardial infarction

addition to standard heparin, clopidogrel, and ASA (acetyl salicylic acid). Heparin infusion was performed throughout the tirofiban infusion. Tirofiban infusion was continued at least 6 hours (6-24 hours) after the PCI. Intervention was performed without tirofiban in the conventional group (group A). The reason for PCI without tirofiban in group A was either the unavailability of the drug at the time of the intervention or operator preference. During the procedure, heparin was given after measuring the ACT. The ACT was kept at a value between 200-300s. All patients received antiplatelet drugs, ticlopidine or clopidogrel, and ASA.

Statistical analysis. The analysis of the results was performed using the Statistical Package for Social Sciences (SPSS, Chicago, Illinois, USA), version 11.5 software for Windows. The categorical variables were shown as number of cases with percentage and continuous variables were shown as mean ± standard deviation. Differences between groups were assessed by Student's t test and the Mann-Whitney U test for continuous variables, as appropriate. Categorical data and proportions were analyzed by use of chi-square test. Paired data before and after PCI were compared

Table 2 - Angiographic characteristics.

Variables	Control group (n=82)	Tirofiban group (n=74)	*P*-value
Culprit lesion			
Left anterior descending coronary artery	31 (37.8)	17 (23.0)	0.001
Left circumflex coronary artery	17 (20.7)	19 (25.7)	
Right coronary artery	33 (40.2)	24 (32.4)	
Saphenous vein/internal mammarian artery	1 (1.2)	14 (18.9)	
Lesion type			
C	40 (48.8)	34 (45.9)	0.723
Non-C	42 (51.2)	40 (54.1)	
Thrombus load			
0	0 (0)	0 (0)	
1	4 (4.9)	2 (2.7)	
2	17 (20.7)	6 (8.1)	0.123
3	22 (26.8)	25 (33.8)	
4	39 (47.6)	41 (55.4)	
Stenosis diameter	84.8 ± 13.8	80.0 ± 11.6	0.061
Obstruction diameter (mm)	0.31 ± 0.28	0.38 ± 0.24	0.124
Reference diameter (mm)	2.70 ± 0.45	2.77 ± 0.37	0.306
Obstruction length (mm)	11.9 ± 3.1	14.7 ± 6.0	0.004

Table 3 - Post percutaneous coronary intervention (PCI) data.

Variables	Control group (n=82)	Tirofiban group (n=74)	*P*-value
TIMI score before PCI	31 (37.8)	18 (24.3)	0.085
0-2			
3	51 (62.2)	56 (75.7)	0.085
TIMI score after PCI			
0-2	19 (23.2)	6 (8.1)	0.015
3	63 (76.8)	68 (91.9)	0.015
Trombus burden			
Pre-PCI	3.17 ± 0.93	3.42 ± 0.76	0.113
Complications	32 (39.0)	8 (10.8)	
Slow flow/no re-flow	17	2	
Coronary dissection	4	2	<0.001
PCI failure	3	2	
Sidebranch plaque shift	6	2	
Acute stent thrombosis	2	0	
Major bleeding	3 (3.7)	4 (5.4)	0.599

Data are expressed as number and (percentage). TIMI - thrombolysis in myocardial infarction.

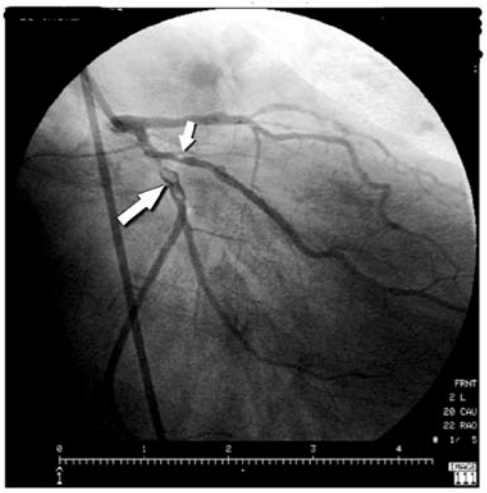

Figure 1 - Coronary angiogram before tirofiban infusion. Arrows indicate massive thrombus in left circumflex coronary artery.

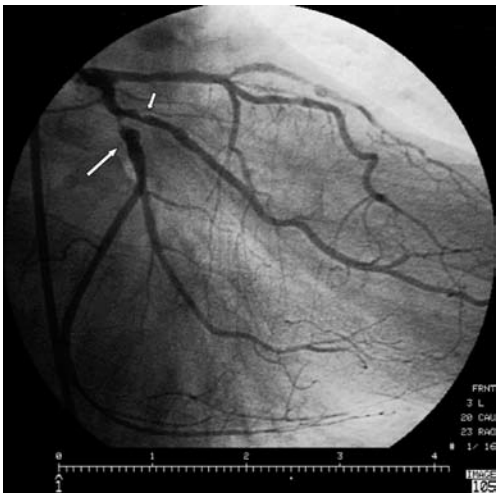

Figure 2 - Complete resolution of thrombus after tirofiban infusion

by McNemar's chi-square test for categorical variables and Wilcoxon test for continuous variables. *P*-values of <0.05 were considered significant.

Results. Clinical characteristics of the patients are listed in **Table 1**. Lesion characteristics are listed in **Table 2**, and angiographic characteristics are listed in **Table 3**. There was no difference between groups regarding lesion location and type. However, ST segment elevation myocardial infarction was more prominent in group A and obstruction length was longer in group B (**Tables 1 & 2**). Although the baseline TIMI 0-2 flow was not different between the groups it is significantly lower in the tirofiban group (group B) compared to group A after the PCI (8.1% versus 23.2%, p=0.015). The decrease in thrombus burden in group B after tirofiban infusion was also statistically significant compared to pre tirofiban levels (1.77±1.05 versus 3.42±0.76, p<0.001). More than 50% decrease in thrombus burden was observed. Group B had better flow characteristics with a 91.9% TIMI 3 flow after PCI (**Table 3**). Intervention was successful in the majority technically, however, no reflow was observed in 17 patients (20.7%) in group A and in 2 patients (2.7%) in group B (p<0.001). There were also 2 acute stent thromboses in group A and none in group B. The lesion could not be crossed via the guidewire in 3 patients in group A and 2 in group B. There was no need for intervention in 9 patients (12%) in group B and in 6 (8%) patients, complete resolution of thrombus was observed after tirofiban infusion (**Figures 1 & 2**). Major bleeding requiring transfusion was observed in both groups A (3 patients) and B (4 patients) due to gastrointestinal bleeding or access site hematomas (3.7% versus 5.4%, non significant).

Discussion. Both long-acting (abciximab) and short acting (eptifibatide, tirofiban) platelet glycoprotein IIb/IIIa inhibitors by inhibiting platelet aggregation prevents arterial occlusion and reduces ischemic complications in the setting of acute ischemic coronary syndromes associated with intracoronary thrombus. Abciximab was shown to be helpful in reducing cardiac mortality and morbidity in the setting of primary and rescue coronary interventions,[3,15,16] without any increase in risk of distal embolization, no re-flow, or abrupt occlusion.[17,18] The local delivery of GPIIb/IIIa receptor blockers was also reported to be successful in thrombus resolution.[19] Prevention of the platelet aggregation effectively with these GPIIb/IIIa receptor blockers avoids further thrombus growth and meanwhile the intrinsic lytic system dominates and lysis the clot. In patients with thrombus dominating non-occlusive lesions, thrombus dissolution could be enough to restore the blood flow as we observed in 9 cases (12.1%) in our study population without any need for percutaneous intervention. Intracoronary thrombus has been shown to be a particularly strong correlate of acute coronary occlusion, and primary thrombus propagation may be more important when dilation is performed in the setting of preexisting thrombus. Dissolution of already formed thrombus may result from the inhibitory effect of GPIIb/IIIa receptor blockers on the plasminogen activator inhibitor (PAI-I), which is associated with enhancement of the natural thrombolytic pathway.[20] The trapping of the thrombus in a highly concentrated drug environment could be one of the possible mechanisms. However, the optimal duration for tirofiban infusion before PCI is still not known. The Platelet Receptor Inhibition in Ischemic Syndrome

Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial[18] demonstrated a decrease in thrombus load with long-term tirofiban infusion in patients with unstable angina. Combination treatment with long-term tirofiban, acetyl salicylic acid, and heparin decreased the thrombus burden by 23% in that patient population. We observed an approximately 50% decrease in thrombus burden in our tirofiban population. Glycoprotein receptor blockers are now well-established adjuncts for both elective PCI and primary angioplasty, and stenting in the setting of AMI.[21,22] These agents led to reductions in death, recurrent MI, or urgent revascularization. However, we believe that these agents have the potential to decrease the thrombus burden in acute coronary syndromes,[23,24] and improve the microvascular perfusion.[25]

Yip et al[26] recently reported a trial regarding tirofiban effect on massive intracoronary thrombus and concluded that tirofiban has no effect on angiographic success; however, we infused the drug for a very short time. The time of tirofiban infusion before PCI in that trial was 25 ± 13.8 minutes, shorter than our trial of 35.3 ±2 5 hours. One of the possible mechanisms leading to higher TIMI 3 flow in our patient population could be the longer duration of tirofiban infusion compared to the trial by Yip et al, which could lead to less thrombus dissolution and inadequate time for the intrinsic fibrinolytic system to dissolve the thrombus. A randomized trial should be conducted comparing long term and short-term tirofiban infusion to determine the best therapeutic strategy in the presence of intracoronary thrombus. Accumulating data in the literature suggests that GPIIb/IIIa receptor blockers could be beneficial in avoiding slow and no reflow in high-risk lesion subsets. However, the data are conflicting. Besides, many trials suggested that tirofiban is inferior to abciximab and needs higher bolus doses than the conventionally suggested. Fuji et al[27] suggested that the majority of thrombus burden is made up of red blood cells rather than platelets and this might explain the ineffectiveness of GPIIb/IIIa receptor blockers in reducing no reflow phenomenon.[27] However, we think that long term infusion could be the key to overcome the ineffectiveness of GPIIb/IIIa receptor blockers by the accumulating effect. We observed less "no re-flow" in our tirofiban group compared to the conventional PCI group mainly due to the longer duration and accumulating effect of the tirofiban. Both treatment strategies, both long-term and short-term, with different loading bolus doses should be compared in a randomized trial. The recently published Acute Catheterization and Urgent Intervention Triage strateg Y (ACUITY) trial[28] looking for an answer for the optimal timing of GPIIb/IIIa receptor blockers also revealed that deferred use of these agents was associated with a slightly higher rate of ischemic events in patients with ACS undergoing PCI. This data also supports the long term accumulating effect of GPIIb/IIIa receptor blockers to obtain a beneficial effect in terms of angiographic features.[28] We think that the question is not any more whether to give these agents, which is a class 1 indication in acute coronary syndromes, but rather for how long or at what dose should we give the drug to obtain the most beneficial result.

In the Do Tirofiban and ReoPro Give Similar Efficacy Trial,[29] tirofiban did not match the early benefit seen with abciximab in PCI patients, a finding attributed to a suboptimal dose. We concluded that high-dose single bolus tirofiban might be as effective as abciximab in patients undergoing PCI with a comparable safety profile.

This is a single center, retrospective, and non-randomized study with small numbers of patients having limitations to be kept in mind before interpreting the results. Randomized studies with larger patient populations should be conducted. In addition, operator discretion could have led to a selection bias depending on the basal flow statuses and thrombus burden regarding the selected procedure.

In conclusion, in our study there was a high angiographic thrombus resolution with long term tirofiban infusion, which also resulted in better TIMI flow grades and less or no reflow after PCI in this highly thrombogenic milieu. Pre PCI long-term tirofiban infusion strategy in thrombus containing lesions seems to be a safe and feasible approach in avoiding "no re-flow" and dissolving the massive thrombus. However, this is a single center, retrospective study with a small number of patients having limitations to be kept in mind before interpreting the results.

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