Original Article

Pretreatment Plasminogen Activator Inhibitor-1 (PAI-1) Level in the Failure of Streptokinase Therapy in Acute Myocardial Infarction

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Abstract

Background: The risk for unsuccessful reperfusion after streptokinase therapy may be caused by the antifibrinolytic effect of platelet-derived type 1 plasminogen activator inhibitor (Pal-1) and antistreptokinase antibodies. This study aims to show the relation of pretreatment PAI-1 levels of patients with acute myocardial infarction treated with streptokinase and the outcome of fibrinolysis, emphasizing on reperfusion with and without considering pretreatment antistreptokinase antibodies.

Methods: Pretreatment PAI-1 and antistreptokinase antibodies levels of 61 patients with acute myocardial infarction, treated with streptokinase, were determined by an enzyme- linked immunosorbent assay kit method. Failure of thrombolysis with streptokinase was present when reperfusion was unsuccessful as assessed by noninvasive reperfusion criteria.

Results: Mean pretreatment PAI-1 level of patients was 29.72 ± 4.74 ng/ml. Thrombolysis with streptokinase failed significantly with higher pretreatment PAI-1 levels ($p < 0.05$) in all patients and patients with negative pretreatment antistreptokinase antibodies.

Conclusion: We showed that higher on reperfusion in patients with acute myocardial infarction, with and without considering pretreatment antistreptokinase pretreatment PAI-1 levels were associated with significant failure of streptokinase therapy with the emphasis antibodies (anti-SK). It seems that by estimating PAI-1>25ng/l and antistreptokinase antibodies higher than normal levels in patients before the start of streptokinase therapy, candidates for potentially unsuccessful streptokinase therapy (with failed reperfusion) can be identified in advance and an alternative therapy such as primary angioplasty with better immediate results can be started.

Keywords: Plasminogen Activator Inhibitor, Streptokinase, Myocardial Infarction.

Impaired fibrinolysis may contribute to the development of coronary artery disease and myocardial infarction[1]. The fibrinolytic activity of blood depends on the balance between the circulating concentrations of tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1), which is both secreted by endothelial cells[2]. Patients with coronary artery disease show increased plasma PAI-1 activity, which diminishes fibrinolytic capacity and thus predisposes to thrombotic disorders including myocardial infarction[3,4,5]. Coronary thrombosis is the major cause of myocardial infarction[6]. Thrombolytic therapy has been shown to reduce mortality and to improve left ventricular function of acute myocardial infarction (AMI) patients[7], [8]. Streptokinase is the most widely used thrombolytic agent because it is effective, easy to administer intravenously, and mainly because it is the cheapest. GUSTO (1993) demonstrated some advantages of tissue plasminogen activator over streptokinase in selected groups of infarct patients: in large anterior infarctions, in the elderly, after bypass surgery, when streptokinase had already been used, and in those who presented within 6 hours of symptoms9.

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One factor that could potentially influence the response to thrombolytic treatment and the occurrence of spontaneous thrombolysis is PAI-110. Ninety percent of PAI-1 is present in platelets. PAI-1 inhibits fibrinolysis by its rapid action as an antiplasmin11-13. A few clinical studies in developed countries have demonstrated that elevated levels of baseline PAI-1 before the start of fibrinolytic treatment are associated with unsuccessful recanalization, because of unsuccessful reperfusion9, 14-18. However there is no data about the role of PAI-1 level on the outcome of patients with acute myocardial infarction treated by streptokinase, heparin, and ASA in Iran and Middle East. On the other hand it has been suggested that pretreatment streptokinase (SK) antibodies reduce the thrombolytic effect, although the results are not consistent19-22. One study in Iran23 showed that not only pretreatment SK antibodies may reduce the thrombolytic effect but also the prevalence of this anti body in Iranian patients was higher than developed countries. We designed this study to investigate the relation of pretreatment PAI-1 levels and the clinical outcome of thrombolysis with streptokinase of Iranian patients with acute myocardial infarction, with and without considering pretreatment antistreptokinase antibodies (anti-SK) with the emphasis on reperfusion.

Materials and Methods

Sixty five patients with acute myocardial infarction that were treated with streptokinase, admitted to the CCU over 12 months, included. Inclusion criteria were precordial chest pain lasting >30 minutes but<12 hours and not responding to two to three sublingual nitroglycerin tablets, associated with 1 to 2 mm of ST-segment elevations in at least two ECG leads[24,25]. Exclusion criteria were contraindication of streptokinase in acute myocardial infarction[24-26].

Four patients whose blood samples for estimation of PAI-1 values were not obtained before the start of streptokinase therapy were excluded. Before the start of therapy, PAI-1 activity of plasma, red blood cell count, platelets, and ceratine kinase (CK) were estimated in the blood samples, from 8:00 AM to 12:00 AM to avoid diurnal variations from the intravenous line in an antecubital veini CK was repeated every 8 hours during the first 24 hours of treatment and an ECG was recorded at the 90 minute after treatment and every 8 hour. On admission, continuous monitoring of rhythm was initiated. Treatment consisted of 325 mg of oral ASA plus an intravenous bolus of 5000 IU of heparin after 6 hour from streptokinase therapy, followed by systemic intravenous high-dose infusion of 1000 IU of heparin per hour during the next 24 hours. ASA at 250 mg per day was given orally during the hospital stay[24-27].

PAI-1 activity of human plasma was determined by an enzyme- linked immunosorbent assay kit (IMUBIND Tissue PAI-1 ELISA Kit) and antistreptokinase were determined with indirect home made ELISA by cutoff assay. During the first 4 to 6 days, the patients were continuously monitored for arrhythmias and cond- uction disturbances. Noninvasive systemic arterial blood pressure was measured hourly and patients were clinically examined twice daily. When necessary, other medications such as nitrates, beta blocker, antiarrhythmic drugs, analgesics, angiote- nsin-converting enzyme inhibitors, digitalis, dopamine, and dobutamine were prescribed at the discretion of the attending physician.

Several studies have shown that ST segment resolution on the EKG is the strong predictor of outcome in acute MI patients and its absence is a better predictor of an occluded rather than patent infarct related artery28, 29. Therefore, in this study we considered successful reperfusion as a ST resolution >50% at 90 min30, 31.

The data were analyzed by nonparametric statistical testing. The values were expressed as mean ± SD, or percentages when it was necessary. Differences between the two groups were tested by chi-square test and Student t test. A P value < 0.05 was considered as statistically significant32

Results

Mean pretreatment PAI-1 level of patients was 29.72 ± 4.74 ng/ml (17.20 to 41.20 ng/ml). Patients were stratified into two groups, according to the final outcome of thrombolysis with streptokinase. Streptokinase therapy was started 5.7±1.23 hr after onset of pain. Baseline clinical characteristics and in-hospital clinical events, with the emphasis on reperfusion and final unsuccessful thrombolysis with streptokinase, were compared between the two groups of patients (table 1). Nonsignificant

Table 1. Baseline characteristic of streptokinase-treated patients divided in two groups: successful and failed reperfusion.

Baseline characteristic	Successful reperfusion	Failed reperfusion
Age (yr)	56.6 ± 5.1	55.8 ± 6.1
Sex (M/F)	25/3	20/2
Hypertension	30%	43%
Diabetes mellitus	20%	28%
Smoking	40%	36%
Hyperlipidemia	30%	25%
Time from onset of chest pain to therapy (hr)	5.5± 1.24	6.5 ±1.43

No significant differences are between groups.

differences in age, sex, previous myocardial infarction, diabetes, CK values at the time of admission, and intervals from onset of chest pain to the start of streptokinase therapy were observed between the two evaluated groups. Significant failure of thrombolysis was demonstrated when pretreatment PAI-1 levels of patients with acute myocardial infarction were higher (31.13 ± 4.04 ng/l, 27.39 ± 4.96 ng/l, P<0.05). Significant failure of thrombolysis also was demonstrated when anti-SK antibody titers were higher (1.97±0.82 times normal control vs. 1.52±0.72 times normal control, P<0.05). Indeed, significant failure of thrombolysis also was demonstrated in 31 patients with negative anti-SK antibody titer when pretreatment PAI-1 levels of this patients was higher (31.25 ± 4.56 vs. 26.98 ± 5.36, P<0.05). Table 2 shows stratification of patients into several group, according to pretreatment PAI-1 level. The groups were compared, according to the outcome of thrombolysis with streptokinase, depending on failed reperfusion. Significant failure of thrombolysis was demonstrated when pretreatment PAI-1 levels of patients with acute myocardial infarction were > 25 ng/l.

Table 2. Stratification of streptokinase-treated patients according to pretreatment PAI-1 levels. Data are frequency and percentage.

PAI-1 (ng/l)	Patients	Reperfusion	Failed reperfusion	Treatment failure
<25	10	7	3	30%
>25	51	17	34	66% *
<30	30	13	17	56.6%
>30	31	9	22	70.9%
<35	53	21	32	60.3%
>35	8	3	5	62.5%

* P = 0.012

Discussion

The delay in reperfusion or resistance to streptokinase therapy and later reoclusions reduce the rate of success of treatment33 - 36. PAI-1, with its antifibrinolytic activity, is thought to participate in treatment failure3, 10,14,16,36. It inhibits spontaneous and pharmacologically induced fibrinolysis and predisposes to subsequent thrombosis with reocclusion of initially recanalized vessel in patients treated with fibrinolytic agents4, 12, 37. Streptokinase activates the fibrinolytic system indirectly by forming a complex with plasminogen, which converts the remaining circulating and thrombus-bound plasminogen into effective plasmin, which is not directly affected by PAI-19, 37. Antifibrinolytic action of PAI-1 upon streptokinase therapy is achieved by local, thrombus-stabilizing effect, thus yielding it resistant to lysis9. PAI-1 inhibits fibrinolysis by its rapid action as an antiplasmin11, 13. In vitro experiments suggest that plasminogen activator inhibitor-1 (PAI-1) is an important determinant of the antifibrinolytic effect of platelets. Circulating PAI-1 activity can represent the marker for the local effects of PAI-19, 12, 13.

We demonstrated that higher pretreatment PAI-1 levels was associated with failed reperfusion in Iranian patients (developing country), this is similar to other studies performed in developed countries9, 14-18. In Sinkovic et al18 study that was performed in a developed country, failure of thrombolysis with streptokinase had been significantly associated with pretreatment PAI-1 levels of >4.0 U/ml. In this study failure of thrombolysis with streptokinase is significantly associated with pretreatment PAI-1 levels >25 ng/l. So, because of significant difference in reperfusion failure when pretreatment PAI-1 levels were > 25 ng/l, by estimating PAI-1 levels of patients before the start of streptokinase therapy, candidates for potentially unsuccessful streptokinase therapy (with failed reperfusion) can be identified in advance and an alternative therapy such as primary angioplasty with better immediate results can be started. Of course, to obtain reliable and more accurate pretreatment PAI-1 level leading to failure

of streptokinase therapy, other studies with larger sample size in the future should be designed. The possible role of anti SK antibodies on failed reperfusion showed in many studies19-22. Therefore anti SK antibodies can probably interact as confounding or obtrusive factor with the effect of high pretreatment PAI-1 levels on reperfusion.

The majorities of previous clinical trials on PAI-1 activity demonstrated the inhibitory effect of PAI-1 on reperfusion in acute myocardial infarction, but, were less clear on the influence of PAI-1 on patients with negative anti SK antibodies titer3, 9, 16, 37.
A significant number of our negative anti SK antibodies titer patients with higher pretreatment PAI-1 levels, developed unsuccessful reperfusion. As a result, it seems that the effect of high pretreatment PAI-1 levels on reperfusion is independent of anti SK antibodies effect.

In conclusion we showed that higher pretreatment PAI-1 levels were associated with significant failure of streptokinase therapy in patients with acute myocardial infarction, with and without considering pretreatment antistreptokinase antibodies (anti-SK) with the emphasis on reperfusion. The critical PAI-1 level for failure of streptokinase therapy, probably is > 25ng/l. Therefore by estimating PAI-1> 25ng/l and antistreptokinase antibodies higher than normal levels before the start of streptokinase therapy, candidates for potentially unsuccessful streptokinase therapy (with failed reperfusion) could be identified in advance and an alternative therapy such as primary angioplasty with better immediate results can be started.

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