

Streptokinase Efficacy in Patients with Acute Myocardial Infarction with Low Level Antistreptokinase Antibody and High Level Lp (a) Lipoprotein

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Abstract

Background- Lp (a) lipoprotein has structural homology with plasminogen and has been shown to inhibit plasminogen activation in vitro and, therefore, the effect of streptokinase (SK). SK's effect is also inhibited by anti-streptokinase antibody (anti SK Ab). We sought to determine whether the serum concentration of Lp (a) lipoprotein present when SK was given in acute myocardial infarction (AMI) influenced the outcome in spite of low anti-streptokinase antibody, as judged by electrocardiography methods.

Methods- Serum Lp (a) lipoprotein concentration was measured in 135 consecutive patients admitted with a diagnosis of AMI who received SK treatment. Recovery and non-recovery from myocardial injury was assessed by the reduction in sum of ST segment elevation measured from the J point (STJ) and Q wave formation in electrocardiography immediately before SK was given compared with two hours later.

Results- Serum Lp (a) lipoprotein concentration was measured within 6 hours of onset of symptoms and before SK was administered, and was higher than that in healthy reference populations. Thirty-one patients with high anti-streptokinase antibody levels were excluded. In patients with Q wave AMI and low anti-streptokinase antibody levels, 31 patients (50%) had high level Lp (a) lipoprotein (34.2mg/dl), whereas patients with non-Q wave AMI and reduction in ST segment elevation after SK >50% (median decrease) had a mean serum Lp (a) lipoprotein concentration of 18mg/dl. The difference was not statistically significant.

Conclusion- In this study, Lp (a) lipoprotein concentration did not significantly influence the outcome of thrombolytic treatment with SK (*Iranian Heart Journal 2008; 9 (1): 34-39*).

Key words: streptokinase ■ lipoprotein ■ myocardial infarction

Almost all cases of acute myocardial infarction (AMI) result from coronary atherosclerosis, generally with superimposed coronary thrombosis.^{1,2} The short-term mortality rate of patients with AMI who receive aggressive pharmacological reperfusion therapy as part of a randomized trial is in the range of 6.5 to 7%,³ whereas observational data suggest that mortality rates in AMI in the community are 15-20%.⁴

In part, this difference relates to the selection of patients without serious comorbidities for clinical trials.

Thrombolysis is well established in the treatment of AMI⁵ and has been shown to increase the patency of the infarct-related coronary artery,⁶ reduce the size of the myocardial infarction,⁷ preserve left ventricular dimensions and function⁸ and reduce both early and late mortality.⁹

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Lp (a) lipoprotein is widely held to be an important risk factor in coronary heart disease. High serum Lp (a) lipoprotein concentrations are associated with an increased prevalence of angina pectoris, myocardial infarction and coronary artery disease assessed angiographically.¹⁰⁻¹³

The Lp (a) lipoprotein has close structural homology with plasminogen¹⁴ and can impede fibrinolysis at the surface of human endothelial cells^{10,11} and breakdown of the fibrin clot. High levels of anti SK Ab also can reduce the effect of SK. We, therefore, investigated the mean range of Lp (a) lipoprotein concentration and the influence of the prevailing serum concentration of Lp (a) lipoprotein on the clinical outcome of AMI treated with SK in low level anti SK Ab patients.

Methods

Between 2002 and 2005, 135 consecutive patients were admitted to our coronary care unit with a diagnosis of definite myocardial infarction and no contraindication to SK. The diagnosis of AMI was based on a history of typical prolonged (>30 minutes) chest pain, plus diagnostic electrocardiography changes of >2mm ST segment elevation in at least two contiguous precordial leads on the admission electrocardiogram or >1mm ST elevation in two or more inferior electrocardiography leads, plus a diagnostic rise in serum cardiac enzymes.^{15,16}

Exclusion criteria were contraindications to SK in AMI,¹⁵⁻¹⁷ bundle branch block, left ventricular hypertrophy and other causes of baseline ST changes not due to AMI. Streptokinase was given as soon as possible once the diagnosis was made, and venous blood was taken at that time for an estimation of serum Lp (a) lipoprotein. Anti-streptokinase Ab was determined with indirect home-made ELISA by cut-off assay.

Thirty-one patients with high levels of anti SK Ab were excluded.

The Lp (a) lipoprotein was determined via a two-site immunoradiometric assay.¹⁸

The second electrocardiogram was performed 1.5 - 2 hours after starting SK. This was compared with the electrocardiogram recorded immediately before SK. Changes in the sum of ST elevation in all 12 leads of the electrocardiogram at the J point (STJ) and 60 ms after the J point were measured. ST segment resolution of 50-70% in the sum of all leads is appropriate for reperfusion, and Q wave formation demonstrates absence of myocardial reperfusion, presumably due to damage to the microvascular bed.¹⁹

Electrocardiograms were performed daily during the 48-hour or longer stay in the coronary care unit and again before discharge from hospital for Q wave formation. Clinical progress of the patients was followed.

The data were analyzed using non-parametric statistical testing. Differences between the two groups were tested by chi-square test or Fisher's exact test (if p value came close to valuable).

Results

In our study, the median serum Lp (a) lipoprotein values were high (34.2 mg/dl). The median value in healthy local people is about 10mg/dl.^{20, 21} The site of the MI on electrocardiographic criteria was inferior in 48%, anterior 45%, posterior in 4% and lateral 3%. The median (range) time between the onset of chest pain and the start of the intravenous infusion of SK was about 2.5 (1-6) hours. From 135 patients, 31 patients with high anti SK levels were excluded because high level anti SK Ab could inhibit thrombolysis.

Patients were stratified into two groups, according to the final outcome of thrombolysis with SK (Table I).

Table I. Baseline characteristics of SK-treated patients divided in two groups: successful and failed reperfusion

Groups	Failed reperfusion	Successful reperfusion
No. (M/F)	62 (41/21)	37 (14/23)
Age (yr)	55/8 + 6/1	56/6+5/1
Hypertension	43%	30%
Diabetes Mellitus	28%	20%
Smoking	36%	40%
Hyperlipidemia	25%	30%

No significant difference was seen between the groups. Five of the 104 patients died during hospitalization.

The median (range) serum Lp (a) lipoprotein concentration in those who died was 28.3mg/dl, which was not significantly different from that of those who survived (34mg/dl).

From 99 patients with low levels of anti SK Ab, 62 patients developed Q waves. Thirty-one patients of those with Q wave MI had high Lp (a) lipoprotein (50%), but the other 31 patients had near normal levels Lp (50%).

From 99 patients, 37 patients with low level anti SK Ab and 50-70% ST segment resolution 90-120 minutes after thrombolysis developed non-Q wave MI. In this group, 12 patients (32.4%) had high levels of Lp (a) lipoprotein and 25 patients (67.6%) had normal Lp (a) lipoprotein levels (Table II).

Table II. Comparison between two groups with Q wave and non Q wave MI with Lp(a) lipoprotein level variation .

MI(N) \ Lp (a) level	NL level Lp (a)	High level Lp(a)
Q-wave MI (62)	50% (31)	50% (31)
Non-Q wave MI (37)	67.6 (25)	32.4% (12)

The groups were compared using the X^2 test or Fisher's exact test. According to the X^2 test, P value was 0.088 (not significant), but as indicated by Fisher's exact test, P value was nearly significant (0.067).

Discussion

Lp (a) lipoprotein is a lipoprotein of unknown physiologic function that is composed of apolipoprotein B-100 (apoB-100), to which apolipoprotein (a) is covalently bound. Increased plasma level of Lp (a) lipoprotein is an independent predictor of the presence of angiographically documented and clinically important coronary artery disease, particularly in patients with hypercholesterolemia and younger than 60 years.^{22,23} Nonetheless, Lp (a) lipoprotein when present at low levels may serve a protective function by binding and participating in the transfer and possible degradation of oxidized phospholipids formed during normal homeostasis or in acutely stressful situations. However, when Lp (a) lipoprotein levels are chronically elevated (as determined genetically), especially in a milieu of chronically increased oxidative stress, Lp (a) lipoprotein, with its content of oxidized phospholipids, may be pro-atherogenic, particularly since it has enhanced binding to the extracellular matrix of the artery wall.²⁴⁻²⁷ In our investigation, the median Lp (a) lipoprotein value within 6 hours of the onset of symptoms of acute myocardial infarction was more than three times that of a healthy population.^{20,21}

It is likely that the Lp (a) lipoprotein value so early in the course of myocardial infarction reflected its premorbid concentration and our study thus supports the view that high levels of Lp (a) lipoprotein are predictive of myocardial infarction. Additionally, because of Lp (a) lipoprotein's resemblance to plasminogen and its lack of activation by known plasminogen activation factors, Lp (a) lipoprotein seems an obvious candidate to

inhibit fibrinolysis competitively. There are *in vitro* studies that show that it will bind to plasminogen receptors²⁸ and to fibrin²⁹ and that it will inhibit plasminogen activation.¹⁴

One attempt to show that Lp(a) lipoprotein does bind to plasminogen receptors *in vivo*, however, proved negative.³⁰ There have been three previous studies in which *in vivo* evidence of an effect of Lp(a) lipoprotein on thrombolysis has been sought with the clinical outcome of patients undergoing thrombolytic treatment for acute myocardial infarction as the model.³¹⁻³³ In none of these reports was SK used, nor was the electrocardiographic response investigated. These studies were small, involving only 20-50 patients, and because coronary angiography could not be undertaken without a clinical indication, they may have been confounded by selection bias. However, Lp(a) has not been found to inhibit fibrinolysis in all *in vitro* studies, which may reflect heterogeneity in Lp(a) isoforms, or differences in experimental conditions.³⁴ *In vivo* studies have yielded inconsistent support of the effect of Lp(a) on fibrinolysis.

To date, most human studies have failed to show an inverse relationship between Lp(a) concentration and fibrinolysis, as measured by several different assays of clot lyses on withdrawn blood samples.³⁵

We postulated that the electrocardiographic response to thrombolytic treatment might provide an insight in the *in vivo* effect of Lp (a) lipoprotein in a larger, less biased series of patients than was possible with coronary angiography.

In none of the studies that reported the role of Lp (a) lipoprotein in thrombolytic therapy outcome was it assumed that anti SK Ab might prevent reperfusion, resulting in the exclusion of patients with high anti SK Ab. Nevertheless, in our study, patients with high anti SK Ab level were excluded and the results were thereafter evaluated.

Our study recall showed no effect of Lp (a) lipoprotein on the patency of infarct-related coronary arteries, but it is a marker for

coronary events in the future, especially in young patients (< 60 yrs).

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