Effect of pretreatment antistreptokinase antibody and streptococcal infection on the efficacy and dosage of streptokinase in acute myocardial infarction

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ABSTRACT

Objectives: The objective of the study is to determine if the presence of antistreptokinase (ASK) antibody in the blood, leads to ineffective thrombolytic therapy with streptokinase (SK) in acute myocardial infarction (AMI) and to investigate if increased dose of streptokinase (2.5 million units) could improve the infarct-related artery (IRA) patency or the clinical outcome in these patients.

Methods: The study was conducted between 1994 and 2001 in 2 institutions; King Fahd Armed Forces Hospital, Jeddah, Saudi Arabia and in Kasr El-Aini Faculty of Medicine, Cairo, Egypt. Fifty consecutive patients with acute myocardial infarction (AMI) were included in this prospective double blind, randomized study. All patients were given the allocated streptokinase dose (1.5 or 2.5 million units) and underwent angiography within 24 hours to establish the anatomy of coronary arteries and the patency of infarct-related artery. Antistreptokinase antibody assay was carried out in a core laboratory.

Results: The study results showed that the presence of ASK antibody or the administration of an increased dose of SK had no effect on improving the patency rate of the infarct-related artery.

Conclusion: The presence of a previous streptococcal infection may not necessarily reduce the effect of SK on the patency of the IRA and/or clinical outcome in patients presenting with AMI. The administration of a larger than currently recommended dose of SK (2.5 million units) did not alter the clinical outcome because it did not improve the patency rate of the IRA. However, a larger study is needed to confirm these observations.

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The routine use of thrombolytic therapy in acute myocardial infarction (AMI) was established in 1986. The results of the first Gissi Trial with over 11,000 patients showed a significant reduction in mortality in patients who received streptokinase (SK) within 6 hours from the onset of symptoms.[1] The usual dose of SK in AMI is 1.5 million units given over 30-60 minutes. The patency of infarct-related artery (IRA) is approximately 50-60% while the rate of reocclusion is approximately 5-20%.[2,3] Rheumatic fever and streptococcal infection are still prevalent in developing countries, which results in high anti- streptokinase (ASK) titer in patients who sustained a previous streptococcal

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infection in these countries.[4] Antistreptokinase titer may interfere with the activity of SK and theoretically may hinder its activity. We examined whether the hypothesis that previous streptococcal infection in developing countries may have a role in determining the appropriate dosage of SK when managing patients with AMI. Therefore, we studied the efficacy of SK with an increased dose of 2.5 million units in patients presenting with an AMI and a high ASK titre.

Methods. Between 1994-1998, we enrolled 50 consecutive patients with AMI in this prospective double blind, randomized study. The patients were from tertiary hospitals in Jeddah, Saudi Arabia (King Fahd Armed Forces Hospital), and Kasr El-Aini Faculty of Medicine, Cairo, Egypt. The collected blood samples were stored at -20°C. All the angiograms were interpreted by independent observers to assess the degree of thrombolysis in myocardial infarction (TIMI) flow. Collation of results and data analysis were not available until 2001, as the study was carried out in 2 different countries. The study protocol was accepted by the ethics committees in the 2 countries.

Antistreptokinase titer antibodies analysis. Samples were taken from all patients before giving SK and sent to the laboratory. They were centrifuged and the serum samples stored frozen at -20°C until it was shipped to a reference laboratory in Germany for analysis. Patients were randomized to receive SK 1.5 million units in Group I (n=25) or to receive SK 2.5 million units in Group 2 (n=25), given in 100ml of normal saline infused over 60 minutes. Hydrocortisone and antihistamines were not considered routine pre-treatment medications and were only given if allergic manifestations developed during SK infusion. Cardiac catheterization was performed within one week after myocardial infarction (MI). Two independent observers assessed TIMI flow in IRA without previous knowledge of patients details or the SK dose. Both observers presented similar assessment in 43 patients; giving a kapps value of 0.628 (Kapps>0.5 means high agreement). An informed written consent was obtained from all patients according to Helsinki guidelines.

Statistical methods. Independent sample t-test was used for quantitative data, and one-way analysis of variance (ANOVA) was used for multivariate analysis. *P* - value was considered significant if <0.05. Chi-Square test was used for qualitative data.

Results. Patients clinical characteristics are summarized in **Table 1**. The mean age was 56.7 ± 11.4 in Group 1 and 54.6±11.0 years in Group 2. The 2 groups had a similar distribution: 22 in group 1 and 23 patients in Group 2 had normal ASK while 3 had a high ASK in group 1 versus 2 in group 2 (*p*=0.52) (**Table 2**). Different types of infarctions were encountered (**Table 1**). Inferior MI occurred in the majority of patients (46%). The number of patients with diabetes mellitus in both groups was 48%. Hypertension (40%) was similar in both groups. Fifty-six percent of all patients were smokers. There was a male predominance, epidemiological data are summarized in **Figure 1**.

The majority of patients (80%) had TIMI flow 3 post thrombolytic therapy, including those with high ASK titer. Patients in Group 2 had a similar TIMI flow even in those with high ASK titer (**Table 2**). Ejection fraction (EF) did not seem to be affected by the presence or absence of ASK or the dose of SK. In Group 1 (40%) and and Group 2 (48%), EF was >50% (**Table 3**).

Discussion. Acute MI is a major cause of morbidity and mortality. Thrombolytic therapy has been a major step in the treatment of AMI.[1] Streptokinase used in clinical practice is prepared from Streptococcal cells. However, Streptococcal infections are common in developing countries and

Table 1 - Site of infarction.

Site	Group 1	Group 2	Total
Inferior	10	13	**23**
Inferolateral	2	1	**3**
Anterior	-	1	**1**
Anteroseptal	8	5	**13**
Anterolateral	5	3	**8**
High lateral	-	2	**2**

Table 2 - Relation between TIMI flow and ASK level.

TIMI	Group 1		Group 2	
	Normal ASK	↑ ASK	Normal ASK	↑ ASK
0	2	0	1	0
1	1	0	1	0
2	2	1	3	0
3	17	2	18	2

TIMI - thrombolysis in myocardial infarction
ASK - antistreptokinase

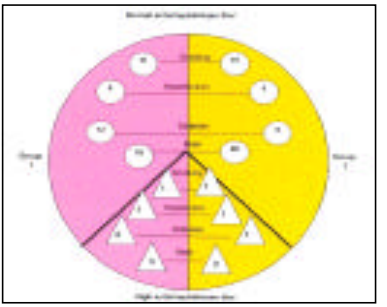

Figure 1 - Epidemiological data of the patients in both groups.

Table 3 - Relationship between EF and ASK level.

Ejection fraction	Group 1		Group 2	
	Normal ASK	↑ ASK	Normal ASK	↑ ASK
31-40	7	1	1	
41-50	5		10	1
51-60	4	1	7	
61-70	6	1	5	
>70				1

EF - Ejection fraction
ASK - antistreptokinase

this theoretically led to the assumption that giving such therapy in developing countries may be less effective. The scientific data supporting the hypothesis are deficient and the scientific basis was not conclusively proven. Patients with previous streptococcal infections behave like SK-treated patients in terms of the reactivity of their platelets to subsequent SK dose in vitro.[5] Anti-streptokinase antibodies arising as a result of previous streptococcal infections are present in the circulation. The prevalence of ASK antibodies in the general population and especially in coronary patients at risk of MI is not well-known and their potentially harmful effects are even less well-known.[6] In a study carried out in India, the pretreatment level of ASK antibodies was found to be more than twice the reported level in Europe and USA. The authors concluded that it might be necessary to reconsider the adequacy of the conventional dosage of SK while treating AMI in the Indian population and possibly in other tropical countries where prevalence of prior streptococcal infection is high.[4]

In this study, we examined the effect of ASK antibodies caused by previous infections on the efficacy of SK given to patients with AMI and we also studied the effects of an increased dose of SK (2.5 million units) on TIMI flow and the clinical outcome. The result was negative with consequently a major clinical impact, since the current and well-accepted guidelines recommend against giving SK within 2 years from previous therapy with SK. In addition, using t-Plasminogen activator is not commonly practiced, simply because of its prohibitive high cost. Thus, the presence of a previous streptococcal infection may not necessarily reduce the effect of SK on the patency of the IRA and/or clinical outcome in patients presenting with AMI. In addition, larger SK dosage did not alter the clinical outcome. The major limitation of the study is the small number of patients who had a positive ASK, but at least ASK is not a major determinant. A larger study is warranted before making such a major recommendation.

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