

Antistreptokinase antibodies and the response to thrombolysis with streptokinase in patients with acute ST elevation myocardial infarction

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ABSTRACT

Background and objective A large number of patients with ST elevation myocardial infarction (STEMI) continue to receive streptokinase (SK) in the developing countries. High levels of antistreptokinase (ASK) antibodies can result in failure of thrombolysis. This study was conducted to assess the presence of ASK antibodies in the general population and its effect on the outcome of thrombolysis with SK.

Design Prospective observational study.

Setting A tertiary care medical institute in Vellore, India.

Patients 148 patients presenting with STEMI undergoing thrombolysis with SK were recruited.

Main outcome measures The response to SK was assessed by reperfusion markers in the patients and they were categorised as good responders, probable responders and non-responders. Those who responded to SK and probable responders were considered to have benefited from thrombolysis.

Results 60 patients (40%) had ASK antibody titres higher than the median. In patients with a window period <6 h, 73% of patients who benefited from thrombolysis had low ASK titres while 100% of the patients who did not benefit had high ASK titres ($p=0.001$). Similarly, in patients with a window period >6 h, 89% of patients who benefited from thrombolysis had low ASK titres while 54% of those who did not benefit had high ASK titres ($p=0.002$).

Conclusions ASK antibodies are present in significant titres in a large proportion of patients in developing countries, which leads to failure of thrombolysis in such patients. In endemic areas with high endemic streptococcal infection, alternative agents should be used for thrombolysis in STEMI.

INTRODUCTION

Ischaemic heart disease is the single most common cause of death in the world. It is no more a disease of the affluent countries and is the most common cause of death in the low and middle income countries.¹ By the year 2020, 40% of all the deaths in the developing countries will be due to cardiovascular causes.² There have been continuous efforts to decrease the mortality and morbidity caused by acute coronary syndromes. The introduction of thrombolysis in the 1980s changed the management of ST elevation myocardial infarction (STEMI) in a big way. The standard management has changed over a period of time to primary angioplasty.^{3,4} However, a large number of patients continue to receive thrombolytic agents for STEMI. This proportion is especially very high in the developing countries because of lack of access to

a cath lab and also the high cost of angioplasty.⁵ Streptokinase (SK) continues to be the first agent of choice in most of the developing countries because of the low cost and familiarity with the drug. SK is an antigenic agent and following exposure is known to induce antibody formation in the body. Many population groups, especially those in areas with high endemic streptococcal infections, have high titres of antistreptokinase (ASK) antibodies even without prior exposure to SK. This has prompted some countries to formulate separate guidelines for thrombolysis in their rural population.⁶ However, not many studies have been done in the developing countries to assess the role of ASK antibodies during thrombolysis with SK. Studies done to check the efficacy of SK in patients who have not been treated with SK earlier but had ASK antibodies have shown conflicting results. This study was hence planned with the following objectives: (1) To assess the presence of ASK antibodies in a patient population in India presenting with STEMI who have not been treated with SK earlier. (2) To assess the efficacy of SK in patients with high ASK antibodies.

METHODS

The study was done as a prospective observational study at a tertiary medical care centre, the Christian Medical College Hospital, Vellore, India, which caters to a large population area. The study protocol was approved by the hospital ethics committee and all the patients gave a written consent before being enrolled for the study.

The patient group included patients presenting with acute STEMI. Inclusion criteria were: first episode of STEMI, age between 20 and 70 years, window period <12 h, not willing for primary angioplasty, no history of prior exposure to streptokinase (SK), no other structural heart disease like rheumatic heart disease or congenital heart disease. Exclusion criteria for the study included: patients presenting with cardiogenic shock, those developing shock or those who died within 30 min of initiation of thrombolysis.

STEMI was diagnosed based on the standard ECG criteria. Venous blood was collected from the patients before the initiation of thrombolysis. Thrombolysis was done with a standard dose of 1.5 million units of SK given over 60 min. The patients were observed for signs of reperfusion. Reperfusion was assessed by the common clinical markers used for this purpose. This included the following: (1) Relief of pain within 90 min on initiation of thrombolysis, (2) ST segment resolution of more

than 50% in two contiguous leads which had the highest ST segment elevation and (3) Reperfusion arrhythmias within 120 min of initiation of thrombolysis. The arrhythmias that were considered were accelerated idioventricular or junctional rhythm, transient second or third degree AV block not needing pacemaker support, acute sinus bradycardia (<50 bpm), ventricular tachycardia or ventricular fibrillation.

Patients who had all three criteria were considered to have responded to SK, those with two criteria as probable responders and those with one or no criteria were taken as non-responders. For a subgroup analysis, the patients were divided into two groups. Those who had a good response and probable responders were considered to have benefited from thrombolysis and those who were non-responders were considered as not having benefited from thrombolysis.

Further, the patients were divided into two groups based on the window period before thrombolysis. Those presenting with a window period ≤ 6 h formed one group while those with a window period > 6 h formed another group.

ASK antibodies were estimated in the serology laboratory by particle agglutination method using a commercial kit—SERODIA-ASK—supplied by FUJIREBIO, Tokyo, Japan. The ASK antibody levels were measured in serial doubling dilutions starting from 0 to 40 and further. Since there are no data to mark a level as high or low, the median value was arbitrarily chosen to divide the group. All patients with values less than the median titre were taken as low antibody levels and all those with values higher than the median were taken as having high antibody levels.

Statistical analysis

All categorical variables were summarised using frequencies and percentages. Cross tabulations were made and association between the variables was assessed either using χ^2 test or Fishers exact test (if the expected cell count was < 5).

RESULTS

A total of 148 patients were recruited for the study. Almost 90% of patients were male subjects. This was partly because female patients were more hesitant to be part of a study. The median age was 52 years. The baseline characteristics of the study population are shown in table 1.

Table 1 Baseline characteristics

	Total n = 148
Percentage of male patients	89.86 (133)
Median age	52 years
Body mass index (mean)	25.11 \pm 2.99
Patients with diabetes mellitus	60.14% (89)
Hypertension	62.84% (93)
History of smoking	55.41% (82)
Mean LDL level (mg/dl)	111.22 \pm 35.44
Mean HDL level (mg/dl)	34.44 \pm 8.24
Mean window period (min)	345 \pm 183.27
Median window period (min)	300
Median ASK titre	320
Number of patients with high titres (%)	60 (40%)
Distribution of infarction territories	Anterior wall—56% (84) Inferior wall—40% (59) Lateral wall—3% (5)

ASK, antistreptokinase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2 Response to SK in patients with a window period ≤ 6 h

Antibody levels	Response to thrombolysis with SK			Total
	Non-responders	Probable responders	Responders	
≤ 320	0 (0%)	17 (30.91%)	38 (69.09%)	55
320+	19 (48.72%)	7 (17.95%)	13 (33.33%)	39

$p < 0.001$.

SK, streptokinase.

Eighty-four patients (56%) had anterior wall STEMI. Ninety-four patients (64%) presented with a window period of ≤ 6 h. The median window period was 5 h. The median ASK antibody titre was 320 units. Sixty patients had high antibody levels.

In patients with a window period ≤ 6 h, most of the patients had a favourable response to thrombolysis. Sixty-nine per cent of patients with low antibody levels had a good response while only 33% of patients with high levels had a good response. All the patients who were non-responders had high antibody levels ($p < 0.001$). In effect, 100% of the non-responders had high antibody titres and only 33% of patients with high titres had a good response to thrombolysis even though they presented relatively early with < 6 h window period (table 2).

In patients with a window period > 6 h, the effect of late presentation could also be seen in the response to thrombolysis. Only 27% of patients with low antibody levels had a good response to SK. But even in this group, among patients with high antibody titres only 5% had a good response to SK while 90% had no response ($p = 0.007$). Thus, even when patients presented late to the hospital, the chances of a response to SK were significantly higher in patients with low antibody levels than in patients with high antibody levels (table 3).

When the data were further analysed to see how many patients had a benefit from thrombolysis some interesting facts were noted. In patients with a window period of ≤ 6 h, all the patients with low antibody levels had a benefit from SK. All the patients who had no benefit from SK had high antibody levels ($p < 0.001$). Only 50% of patients with high antibody levels had a benefit from SK (table 4).

In patients who had a window period of > 6 h, slightly more than 50% of patients with low levels had a benefit from SK and they formed almost 90% of the total number of patients who had a benefit from SK in this group. Ninety per cent of patients with high antibody levels had no benefit from SK ($p = 0.002$) (table 5).

DISCUSSION

This study shows clear evidence that (1) the study population, in a developing country like India, had significantly high levels of ASK antibodies and (2) high levels of ASK antibodies in the serum led to failure of thrombolysis in these patients.

Thrombolysis continues to be the most common mode of revascularisation for patients with STEMI in developing countries.⁵ Even though many newer thrombolytic agents have been introduced, SK continues to be the most commonly used

Table 3 Response to SK in patients with a window period > 6 h

Antibody levels	Response to thrombolysis with SK			Total
	Non-responders	Probable responders	Responders	
≤ 320	16 (48.48%)	8 (24.24%)	9 (27.27%)	33
320+	19 (90.48%)	1 (4.76%)	1 (4.76%)	21

$p = 0.007$.

SK, streptokinase.

Table 4 Benefit of SK in patients with a window period ≤ 6 h

Antibody levels	Benefit with SK	
	No	Yes
≤ 320	0 (0%)	55 (73.33%)
320+	19 (100%)	20 (26.67%)
Total	19	75

$p < 0.001$.
SK, streptokinase.

thrombolytic agent in the low income countries because of its significantly lower cost. SK however is an antigenic drug and once exposed, patients develop antibodies against it.⁷ These antibodies persist for years after the treatment and make these patients resistant to any further treatment by SK. Though the exact duration for which these antibodies persist is not known, it is at the least 2 years.⁸⁻⁹ Accordingly, both the American College of Cardiology and European Society of Cardiology guidelines mention a previous treatment with SK as a contraindication for SK use in patients with STEMI.^{3,4}

However, many studies have shown that in some population groups, the level of ASK antibodies is significantly high even without any previous treatment with SK. Lynch *et al* showed that in the developed world significant ASK antibodies are present in a very small percentage of patients presenting with STEMI.¹⁰ Studies have been conducted to assess the impact of these antibodies on the outcome of thrombolysis with SK. Some studies have suggested that the presence of these antibodies do not affect the outcome of thrombolysis with SK.¹¹⁻¹² However, an overwhelming number of studies have proven the failure of thrombolysis in patients with high ASK antibodies. Guidelines however continue to recommend the use of SK for thrombolysis, as significant titre is present in a very small percentage of population in the Western countries.¹⁰ However, in areas with high endemic streptococcal infections, very high titres of ASK antibodies are present in the serum.¹³⁻¹⁵ Presence of high titres of ASK antibodies has also been shown in the Indian population which is also likely to be due to the same reason.¹⁶ Though, by implication, it is safe to predict that SK is likely to fail in the majority of patients from these geographical areas, not many studies have proven this in the actual clinical scenario. Most of the studies which showed failure of SK were in patients who were earlier treated with SK and consequently had high ASK antibodies. Another earlier study which proved this fact was also done in a Western population.¹⁷ Our study is the first to prove this hypothesis in a geographical area with high endemic streptococcal infections and also had a larger group of patients.

The gold standard to diagnose a failed thrombolysis would have been a coronary angiography; however, it was not possible for us to do an angiography for all the patients because of limited resources. The clinical markers used by us have been widely used and continue to serve as criteria for patients to undergo a rescue angioplasty.^{3,18,19} We also divided the patients into two separate groups depending on the time of presentation as the success of thrombolytic agent depends significantly on the

time of presentation. This study showed that the effect of ASK antibodies is present on both the groups.

The implications of the study can be profound, especially in the developing countries with high endemic streptococcal infections. Current guidelines advocate the use of any thrombolytic agent including SK for thrombolysis in acute STEMI. However, it would be prudent to suggest that in areas likely to have high ASK titres, SK should not be used for thrombolysis and the newer thrombolytic agents should be used. In countries with limited access to primary angioplasty, the importance of thrombolysis cannot be emphasised more. A thrombolytic agent with high chances of failure can hardly be recommended in such a setting. More studies need to be done with larger number of patients before we change the guidelines but available data do suggest a cautious use of SK in certain areas. Again, what antibody level can be labelled as a high titre of antibody needs to be defined. This will need large population based studies to assess antibody titre beyond which it is likely to fail.

CONCLUSION

ASK antibodies are widely prevalent in high titres in the general population in developing countries and in areas with high endemic streptococcal infections. Thrombolysis with SK is usually not successful in such patients. Hence, in a population likely to have high ASK antibodies, SK should not be used for reperfusion in patients with STEMI. Instead, the newer thrombolytic agents should be used where a primary angioplasty is not an option.

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Competing interests None.

Patient consent It was only an observational study and there was no study related intervention or pharmacological measure taken. Identity of none of the patients is revealed.

Ethics approval Approval provided by the Institute Review Board and Ethics Committee, CMC Vellore, India.

Provenance and peer review Not commissioned; internally peer reviewed.

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Table 5 Benefit of SK in patients with a window period > 6 h

Antibody levels	'Benefit' with SK	
	No	Yes
≤ 320	16 (45.71%)	17 (89.47%)
320+	19 (54.29%)	2 (10.53%)
Total	35	19

$p = 0.002$.
SK, streptokinase.

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