THROMBOLYTIC FAILURE WITH STREPTOKINASE IN ACUTE ST ELEVATION MYOCARDIAL INFARCTION USING ELECTROCARDIOGRAM CRITERIA AT CORONARY CARE UNIT OF CHITTAGONG MEDICAL COLLEGE HOSPITAL

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Summary

Thrombolysis is the commonest modality of revascularization and Streptokinase is the most widely used thrombolytic agent in Bangladesh. The thrombolytic efficacy of streptokinase has been found to be low (50-60%) in various international studies and its efficacy in our population requires to be investigated. ST-segment resolution 90 minutes after thrombolysis is an excellent marker of successful myocardial reperfusion having good sensitivity and specificity and thus can be used as an effective tool to determine reperfusion success. This study aimed to determine the thrombolytic failure with streptokinase in acute ST elevation myocardial infarction using 90 minute ST resolution on electrocardiogram and to compare the failure rate in this study with that found in other studies. This cross sectional observational study was conducted amongst the patients admitted in the coronary care unit (CCU) at Chittagong Medical College Hospital (CMCH) during September 2011 to February 2012. An ECG was performed at admission and 90 minutes after starting streptokinase infusion. Thrombolytic failure with streptokinase was defined using electrocardiogram criteria of less than 50 percent reduction in ST elevation in the worst infarct lead after 90 minutes of streptokinase infusion. Univariate analysis was used to test association of clinical variables with study outcome. A total of 82 patients (82 percent) failed thrombolysis using streptokinase. The failures were associated with four variables in univariate analysis model including anterior location of myocardial infarct (p-value < 0.001), longer symptom onset-to-needle time (p-value is 0.02), hypertension (p-value is 0.03) and diabetes (p-value is 0.03). Failure rates were higher compared to four international trials (GUSTO-1- 46%, Chen et al-76%, Lee et al-56.8%, Riffat Sultana et al-38.5%). The failure rate was higher compared to that found in some of the international studies done both in Asian and western population which could be due to higher prevalence of streptococcal infection and hence anti-streptococcal antibody in our population. This group of patients may benefit from other early reperfusion strategy like recombinant tissue plasminogen activator (tPA) or primary PCI within 1 to 2 hours.

Key words

Electrocardiogram criteria; myocardial infarction; reperfusion failure; ST resolution; streptokinase; thrombolysis.

Introduction

Acute ST-segment elevation myocardial infarction (MI) is caused by coronary plaque rupture/erosion and resultant thrombosis leading to an occluded epicardial infarct-related artery (IRA) [1,2]. Timely fibrinolytic therapy can re-establish coronary flow in this setting and salvage jeopardized myocardium. Large randomized clinical trials (RCTs) as well as the Fibrinolytic Therapy Trialists overview have clearly demonstrated a statistically significant mortality benefit with thrombolytic therapy over placebo in this clinical setting [1,3]. Despite dramatic strides in the area of percutaneous intervention, thrombolysis remains the most utilized form of reperfusion treatment worldwide. A review by fibrinolytic therapy trialists' (FTT) group has shown that thrombolysis prevents 20–30 deaths per 1,000 patients with 25- 50% reduction in mortality [3].

In Bangladesh and some other developing countries, streptokinase as a thrombolytic is assumed the first and the most important therapeutic intervention for reperfusion, which best matches the socioeconomic status of most patients and healthcare infrastructure. Coronary angiography was the gold standard to determine Coronary artery patency after reperfusion therapy but it was expensive, invasive and not always available early. Therefore, bedside noninvasive markers were more attractive options.

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Among these, electrocardiogram (ECG) had good predictive value and sensitivity. It was also easily available and cheap. Sutton et al showed that less than 50% resolution of ST segment elevation in the worst infarct lead had a sensitivity of 81%, specificity of 88% and positive predictive value of 87% to predict less than TIMI-3 flow [4]. The ST-segment resolution stratified by Schroder into 3 categories (complete resolution, ≥70%; partial resolution, 30–70%; and no resolution, <30%) after reperfusion therapy has been identified as a prognostic indicator for patients with acute myocardial infarction (AMI) [5].

Reperfusion therapy in STEMI is the most important component of treatment, as it strongly influences short and long-term patient outcome. The main objective of healthcare providers should be to achieve at least 75% of reperfusion therapy applied to patients of STEMI in a timely manner, and preferably within the first 3 hours after onset of symptoms [6].

While ideally patients should receive streptokinase as soon as possible after symptom onset, late benefit has been observed in patients presenting up to 12 hours after pain onset, as is often the case with the elderly. Indeed, in patients treated > 6 hours after infarct in the GUSTO (Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded Arteries) trial, streptokinase produced lower mortality results than accelerated recombinant tissue plasminogen activator (rt-PA). However, in contrast to the similar effects of streptokinase and conventionally administered rt-PA on overall survival demonstrated in previous large trials, the GUSTO study showed a lower mortality rate for accelerated rt-PA than for streptokinase in the elderly and in the total patient population [7]. The most frequent adverse effects associated with streptokinase therapy are haemorrhagic complications, with an incidence of 0.4% for major bleeding (requiring transfusion) and 3.6% for minor bleeding among the total population in the GISSI-1(Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) and ISIS-2 (International Study of Infarct Survival-2) trials [8]. Streptokinase is prepared from various streptococcal species which cause different streptococcal infections in humans with resultant serotype specific antibody production. As streptococcal infection is common in our country, high levels of antistreptokinase antibody can be anticipated. Therefore there is a possibility of reperfusion failure [9]. As streptokinase is imported to our country, the expiration date, the quality and brand and the volume of its effective material should also be checked [14].

This study aims to determine the failure rate of thrombolysis with streptokinase in acute ST elevated myocardial infarction (AMI) using ECG criteria, its association between various independent clinical variables and comparison of failure rates with other studies.

Materials and methods

This was a cross sectional observational study done at the Coronary care unit of Chittagong Medical College Hospital on patients with acute STEMI duri. The inclusion criteria were STEMI patients admitted to the coronary care unit with Chest pain of ≤12 hours but >30 minutes duration and ECG evidence of transmural ischemia (1–2 mm ST-segment elevation in ≥ 2 limb leads and/or ≥ 2 mm ST-segment elevation in ≥ 2 precordial leads) . Exclusion criteria were AMI with Bundle branch block, Non-ST elevation myocardial infarction(NSTEMI), Streptokinase given in other hospitals within 5 years, Symptom-to-needle time of > 12 hours, contraindications to Streptokinase therapy (streptokinase administration within the previous 2 years, allergy to the drug, surgery or cerebrovascular accident within previous 6 weeks, Warfarin therapy, active peptic ulcer disease, bleeding disorders, uncontrolled hypertension), patients with cardiogenic shock, patients unwilling to give consent and history of sore throat or pharyngitis within 3 to 6 months. Main outcome variables to be studied were: Age, Gender - male / female, Symptom onset to needle time, Infarct locatio, Hypertension, Diabetes mellitus and Smoking history. Acute ST elevation nyocardial infarction was defined as Characteristic ischaemic chest pain and ECG evidence of transmural ischemia (1–2 mm ST-segment elevation in ≥ 2 limb leads and/or ≥ 2mm ST-segment elevation in ≥ 2 precordial leads).Thrombolytic failure was defined as less than 50% resolution of ST segment elevation in the worst infarct (highest ST elevation) lead. Streptokinase infusion was given as per protocol at the standard dose of 1.5 MU over 60 min. One vial (1 500 000 IU per vial) of streptokinase was reconstituted with 5 ml of 0.9 % normal saline and then added to 50 ml of 0.9 % normal saline. This was infused through an intravenous line over 60 min using a JMS infusion set with 50 ml buret. Intravenous hydrocortisone 200 mg bolus was given prior to the administration of streptokinase. Infusion was stopped if there was a drop of blood pressure below systolic blood pressure of 90mmHg or if asthmatic attacks developed and was restarted slowly. The first ECG was recorded prior to starting streptokinase, and the second ECG was then

recorded after completion of streptokinase infusion. This was usually after 90 min, but a time window of 2–4 hours were allowed.

Vertical height of ST segment elevation in the lead with the maximum ST segment elevation (worst infarct lead), before and after streptokinase, was measured using a caliper and a standard ruler in mm. The ST segment was measured 80 ms from J point, which corresponded to the peak of ST elevation.

J point was defned as the first turning point in the ST segment on ECG. Failure of thrombolysis with streptokinase was defined as less than 50% reduction in ST segment elevation after 90 min (time window 2–4 hours) in the worst infarct lead with no idioventricular rhythm.

All data was collected by using a pre formed data collection sheet. Data analysis was conducted using the Statistical Package for Social Sciences version 16 (SPSS Inc, Chicago, IL, USA). Numerical data was recorded as mean and standard deviation, and categorical data as percentages. The numerical and categorical variables used in this study were chosen based on previous clinical studies [10,11,12,13].

A p-value of less than 0.05 was considered signifcant association with thrombolysis failure using streptokinase. Univariate analysis using chi-square test for categorical data and Student's t-test for numerical data were used to compare the association of variables.

The results of univariate analysis were recorded as p-value.

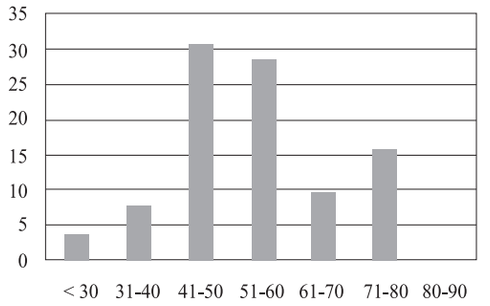
Results

A total of 100 patients with acute ST elevation MI and received streptokinase infusion were recruited between September 2011 to February 2012. This study was conducted in the cardiology department of the Chittagong Medical College Hospital. There were a total of 82 patients (82%) who had failed thrombolysis with streptokinase compared to 18 patients (18%) who had a successful thrombolysis (Table I).

A total of 10 independent variables were included in the univariate analysis (Table I). The study consisted of 78 males (78%) and 22 females (22%). The mean age was 53.3 (SD ±13.7) years.

There were more patients with anterior location of infarct (51; 51%) and who had a significant association with failure of thrombolysis using streptokinase ($p < 0.001$). The mean symptom onset to needle time was 372 minutes. A longer onset to needle time was significantly associated with failure of thrombolysis using streptokinase ($p = 0.02$; 95% CI 1.00–1.02). Patients with a history of diabetes mellitus (31; 31%) and AMI had increased risk for thrombolysis failure using streptokinase, and this association was significant (95% CI 1.13–8.69; $p = 0.03$). A total of 48(48%) of the AMI patients who received streptokinase had prior history of hypertension. The past history of hypertension had increased risk of failure of thrombolysis with streptokinase (35; 72.82%) which was significant($p=0.03$). There were more current smokers (54;54%), but no association was noted between the current smoking status and failure of thrombolysis with streptokinase ($p>0.05$).

The failure rate observed in this study was higher compared to four other international studies (GUSTO-1- 46%, Chen et al-76%, Lee et al-56.8%, Riffat Sultana et al-38.5%). Results were closest to Chen et al (76%), a study done on Asian population [10].



Range = 27-80 years

Mean ± SD = 53.30 ± 13.70

Fig 1 : Age distribution of STEMI patients.

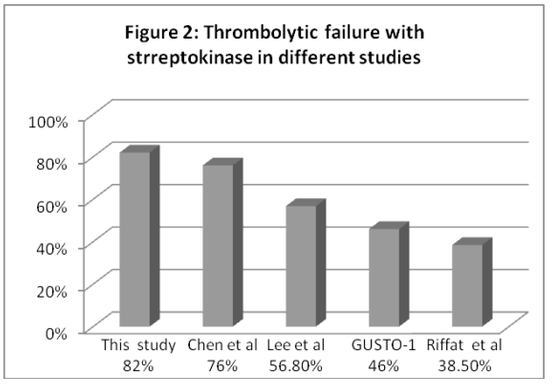


Fig 2 : Thrombolytic failure with strreptokinase in different studies.

Table I : Univariate analysis model in predicting association between independent variables and outcome parameters with failure of thrombolysis using streptokinase in acute myocardial infarction.

Independent Variables	Total n=100	Success n (%)	Failure n (%)	P value
Total patients	100	18 (18%)	92 (92%)	
Male	78	12(15.11%)	66(84.89%)	>0.05^{NS}
Female	22	6(27.33%)	16(72.67%)	>0.05^{NS}
Smoker (current and past)	67	23(34.33%)	44(65.67%)	>0.05^{NS}
Hypertension	48	13(27.18%)	35(72.82%)	0.03**
Diabetes	31	8(25.77%)	23(74.23%)	0.03**
Peripheral vascular disease	16	3(18.75%)	13(81.25%)	>0.05^{NS}
Previous angina	63	12(19 %)	6(81 %)	>0.05^{NS}
Previous MI	8	1(12.51%)	7(87.49%)	>0.05^{NS}
Symptom onset to needle time ≤4 hours	38	16(42.10%)	22(57.90%)	0.02**
4-8 hours	44	02(4.50 %)	42(95.50%)	0.02**
8-12 hours	18	00(00%)	18(100 %)	0.02**
Anterior infarct	51	6(11.76 %)	45(88.24%)	<0.001***
Inferior infarct	47	12(25.53%)	35(74.47 %)	<0.001***
Lateral infarct	2	0(00 %)	2(100%)	<0.001***
Heart failure, Killip class >1	19	4(21.05 %)	15(79.95%)	>0.05^{NS}

NS= Not significant **/***= Significant (<0.05)

Discussion

The failure rate for thrombolysis with streptokinase was 82% (18% success) in AMI, when using the ECG criteria. The results were in concordance with Chen et al where the incidence of complete, partial, and no ST resolution was 24%, 27%, and 49% respectively [10]. The study however was not concordant with other studies where the success rates were 54% in the multicentre GUSTO-I trial, 61.5% in Riffat Sultana et al and 43.2% success in Lee et al trials [7,11,12].

Patients with anterior location of infarct had a worse clinical outcome, compared to inferior infarct. Large clinical trials, including GUSTO-I, showed that streptokinase in patients with anterior infarct was associated with lower mortality and morbidity [7]. However, subsequent studies including INJECT also showed that patients with anterior infarct achieved less reperfusion success compared to inferior infarct when given thrombolytic agent [15]. Our study has shown that anterior infarct was associated with higher thrombolysis failure with streptokinase, which was compatible with other studies [10,11,12,15].

In this study, 62 % of cases presented to the emergency department after four hours of symptoms and of these, 60 (96.44%) had failed thrombolysis with streptokinase. Myocardium loss is the greatest within the first one hour from onset of symptoms, and the optimal time of thrombolysis was recommended at 70 minutes in the INJECT trial [15]. According to Lee et al for every one minute increase in door-to-needle time, there would be an increase in risk of failure of thrombolysis with streptokinase by an additional 10% [12]. This study was not intended to look into the causes of longer door-to-needle time, but possible reasons included inappropriate initial triage, delay in transport, missed initial diagnosis and delay in starting treatment.

Although only 31% of the cases were diabetic patients, 76.7% of the diabetic patients did not achieve successful thrombolysis using streptokinase with thrice the risk of failure. The reasons for the higher risk of failure were the diffuse and multiple small vessel diseases in diabetic patients, which did not respond well to streptokinase. Diabetic patients usually present to the hospital later, due to their impaired sensation in myocardial ischaemic pain.

Hypertension is a known risk factor for higher mortality in patients who had AMI, and it is additive to other known risk factors, as shown in the Framingham study [16,17]. Large international trials had showed that hypertension remained as an important predictor of mortality in the thrombolysis era, including GUSTO-I and GISSI-2 [7,8].

A total of 48% cases were hypertensive in this study. Most of the hypertensive cases (72.9%) did not achieve thrombolysis with streptokinase and the risk was threefold. Possible reasons for the higher failure rate were poorly-controlled hypertension, high-risk nature of hypertension, and possible accelerated atherosclerosis associated with endothelial dysfunction.

Current smokers have an increased risk of thrombolysis failure with streptokinase, as shown in other studies, but this did not reach significance in this study [18]. The possible explanation is the “smoker’s paradox” theory, where current smokers were shown to have earlier presentation to the hospital and therefore achieved a better outcome of thrombolysis compared to the nonsmokers.

Streptokinase is prepared from various streptococcal species which cause different streptococcal infections in humans with resultant serotype specific antibody production. As streptococcal infection is common in our country, high levels of antistreptokinase antibody can be anticipated. Therefore there is a possibility of reperfusion failure [9].

Streptokinase is a first generation thrombolytic agent. It acts by complexing with plasminogen and it is not fibrin specifc. Eventually there will be depletion of plasminogen, known as “plasminogen steal”, which will limit the fibrinolytic action accounting partly for the thrombolysis failure [19].

In addition, streptokinase was shown to have the highest paradoxical thrombin activation (or “thrombolytic paradox”), when compared to other thrombolytic agents [20]. Thrombolytic paradox was due to the pro-coagulant effect of thrombolytic agent despite its action of lysing the clots. The main hypothesis for the pro-coagulant effect was due to plasmin-mediated activation of the contact system of the coagulation pathway (Kallikrein/factor XII), as coined by Ewald and Eisenberg in 1995 [21].

Even with the same thrombolytic agent, different doses and administration regimens and concomitant use of adjunctive agents can cause variations to the patency rates signifcantly [19]. There are different preparations of streptokinase in the market and it is possible that each of them may have different effects to arterial patency rates.

In addition, the fixed dose of 1.5 MU used across major streptokinase trials, including GISSI-I and GUSTO-I, may have different responses among different races, gender and age groups [7,8].

Conclusion

The results of the present study indicate that streptokinase had a high (82%) failure rate of thrombolysis among ST elevation AMI patients. The failure rate was higher compared to that found in other studies. Therefore other reperfusion strategies should be considered, especially in the high-risk patients. Newer generation thrombolytic agents include the tissue plasminogen activators (tPA) (e.g. alteplase and reteplase). These are associated with a better thrombolysis outcome compared to streptokinase. However, these agents are expensive and not always available in resource-poor areas.

Another strategy is PCI, which in many prospective trials, have shown better mortality outcome compared to thrombolytic agents(95% TIMI-3 flow reperfusion compared to 50-60% with thrombolytics) and can be an alternative choice in centers with facilities to provide it.

A recently published study has proven that PCI was associated with better reperfusion and mortality outcome compared to streptokinase in patients with anterior AMI (relative risk 1.6, p = 0.03) [22].

Another option would be rescue angioplasty. There are three randomised trials that suggested rescue angioplasty offered benefit, although the data is not compelling as yet [23].

Disclosure

All the authors declared no competing interest.

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