Thrombolysis Failure with Streptokinase in Acute Myocardial Infarct using ECG criteria – HUSM experience

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LIST OF ABBREVIATIONS

3VD	:	Three vessel disease
ACE	:	Angiotensin converting enzyme
ACS	:	Acute coronary syndrome
AMI	:	Acute myocardial infarct
BP	:	Blood pressure
bpm	:	beats per min
CABG	:	Coronary artery bypass graft surgery
CI	:	Confidence interval
CPR	:	Cardiopulmonary resuscitation
DBP	:	Diastolic blood pressure
ECG	:	Electrocardiography
HF	:	Heart failure
HR	:	Hazard ratio
HUSM	:	Hospital Universiti Sains Malaysia
LAD	:	Left anterior descending artery
LBBB	:	Left bundle branch block
LCx	:	Left circumflex artery
LMS	:	Left main stem
min	:	Minutes
OR	:	Odds ratio
RCA	:	Right coronary artery
ROC	:	Receiver operating characteristics curve

n	:	number
NSTEMI	:	Non-ST elevation myocardial infarct
Ref	:	Reference
PTCA	:	Percutaneous coronary angiography
PCI	:	Primary coronary intervention
SBP	:	Systolic blood pressure
SD	:	Standard deviation
SE	:	Standard error of mean
TIMI	:	Thrombolysis in myocardial infarct
tPA	:	tissue plasminogen activator
UA	:	Unstable angina
WHO	:	World Health Organization

Abstrak

Kadar kegagalan trombolisis dengan streptokinase adalah tinggi di kalangan pesakit serangan jantung walaupun harganya lebih murah dan lebih luas dipergunakan. Kriteria ECG yang menggunakan lebih daripada 50% pengurangan ketinggian segmen ST di lead infarct yang paling teruk adalah sensitif dan spesifik dalam menjangka aliran TIMI 3.

Objektif utama kajian ini adalah untuk menentukan kadar kegagalan trombolisis dengan streptokinase menggunakan kriteria ECG di Hospital Universiti Sains Malaysia (HUSM). Objektif kedua adalah untuk menentukan sama ada kegagalan trombolisis dengan streptokinase mempunyai hubungan dengan pembolehubah tak bersandar, parameter rawatan dan parameter kekerapan sindrom akut koronari dan kadar kematian selepas satu tahun.

Sejumlah 192 pesakit terlibat dalam kajian kohort retrospektif ini. Sejumlah 109 (56.8%) pesakit gagal trombolisis dengan streptokinase. Terdapat 7 pembolehubah dalam analisis univariate yang menunjukkan hubungan dengan kegagalan trombolisis dengan streptokinase. Ini termasuklah lokasi anterior MI ($p<0.001$), masa simtom-ke-jarum yang lebih lama ($p=0.01$), masa pintu-ke-jarum yang lebih lama (min 114 $\pm$ 82.9 minit, $p=0.03$), sejarah hipertensi ($p=0.04$), kadar denyutan nadi yang lebih tinggi (min 79.3 $\pm$ 18.3 denyutan per minit, $p=0.01$), tekanan sistolik yang lebih tinggi (min 136.7 $\pm$ 28.9 mmHg,

p=0.02) dan tekanan diastolik yang lebih tinggi (min 83.8 ± 20.9 mmHg, p=0.003). Manakala, terdapat 5 pembolehubah dalam analisis multivariate yang menunjukkan hubungan dengan kegagalan trombolisis dengan streptokinase. Ini termasuk lokasi anterior MI (p<0.001; OR 0.07, 95% CI 0.03 – 0.16), masa pintu-ke-jarum yang lebih lama (p=0.02; OR 1.01, 95% CI 1.00 – 1.02), sejarah kencing manis (p=0.03; OR 3.13, 95% CI 1.3 – 8.69), sejarah hipertensi (p=0.08; OR 2.06, 95% CI 0.92 – 4.60) dan jumlah sel darah putih yang lebih tinggi (p=0.03; OR 1.12, 95% CI 1.01 – 1.24). Selain itu, analisis univariate juga menunjukkan bahawa kekerapan sindrom akut koronari (p=0.02; OR kasar 2.49, 95% CI 1.16 – 5.32) dan kadar kematian selepas satu tahun yang lebih tinggi (p=0.04; OR kasar 7.61, 95% CI 0.95 – 61.24) adalah berkaitan dengan kegagalan streptokinase sebagai agen trombolisis di kalangan pesakit serangan jantung.

Keputusan kajian ini menunjukkan bahawa streptokinase mempunyai kadar kegagalan trombolisis yang tinggi dengan menggunakan kriteria ECG di Hospital Universiti Sains Malaysia (HUSM). Terdapat 5 pembolehubah yang menunjukkan hubungan erat dengan kegagalan trombolisis dengan streptokinase. Ini termasuklah lokasi anterior MI, masa pintu-ke-jarum yang lebih lama, sejarah kencing manis, sejarah hipertensi dan jumlah sel darah putih yang lebih tinggi. Pesakit dengan pembolehubah-pembolehubah ini boleh dirujuk lebih awal untuk strategi reperfusi yang lain termasuklah tPA, PCI dan CABG.

Abstract

Streptokinase has high thrombolysis failure rate despite being cheap and widely used in acute myocardial infarction. Electrocardiogram criteria using more than 50% reduction in ST elevation in the worst infarct lead predicted TIMI III flow with good sensitivity and specificity.

The primary objective of this study was to determine the failure rate of thrombolysis with streptokinase in acute myocardial infarction using electrocardiogram criteria in Hospital Universiti Sains Malaysia (HUSM). The secondary objective was to compare the association between independent variables, treatment and outcome parameters with failure of thrombolysis with streptokinase.

A total of 192 subjects were recruited into this retrospective cohort observational study. 109 patients (56.8%) has failed thrombolysis with streptokinase. Seven variables were significantly associated with thrombolysis failure using streptokinase in a univariate analysis including anterior location of myocardial infarct (p<0.001), longer symptom-to-needle time (p=0.01), longer door-to-needle time (mean 114 ± 82.9 min, p=0.03), history of hypertension (p=0.04), higher heart rate (mean 79.3 ± 18.3 beats per min, p=0.01), higher systolic blood pressure (mean 136.7 ± 28.9 mmHg, p=0.02) and higher diastolic

blood pressure (mean 83.8 ± 20.9 mmHg, p=0.003). Five variables were associated with streptokinase failure as thrombolytic agent in multiple logistic regression analysis (backward stepwise method) including anterior location of myocardial infarct (p<0.001; OR 0.07, 95% CI 0.03 - 0.16), longer door-to-needle time (p=0.02; OR 1.01, 95% CI 1.00 – 1.02), diabetes mellitus (p=0.03; OR 3.13, 95% CI 1.13 – 8.69), hypertension (p=0.08; OR 2.06, 95% CI 0.92 – 4.60) and high total white cell count (p=0.03; OR 1.12, 95% CI 1.01 – 1.24). Both recurrent acute coronary syndrome (p=0.02; crude OR 2.49, 95% CI 1.16 – 5.32) and death after one year (p= 0.04; crude OR 7.61, 95% CI 0.95 – 61.24) were associated with increase in the rate of thrombolysis failure with streptokinase in univariate analysis.

In conclusion, the result of this study has shown that streptokinase has higher failure rate of thrombolysis in acute myocardial infarction using electrocardiogram criteria in HUSM. History of diabetes mellitus, history of hypertension, anterior location of myocardial infarction, longer door-to-needle time and high total white cell count were highly predictive of increase in the rate of thrombolysis failure using streptokinase. This group of patients may benefit from other early reperfusion strategy including tissue plasminogen activators (tPA), PCI or CABG.

Chapter 1

1.0 Introduction

Cardiovascular disease is the commonest cause of death in our government hospitals accounting for 24.5% of all deaths for the year 1998 alone. Coronary heart disease accounts for a majority of these deaths (Kementerian Kesihatan Malaysia 1990-1998).

Acute myocardial infarct is death of cardiac muscle following acute coronary occlusion due to fissuring of atherosclerotic plaques. Thrombolytic therapy use is aimed at achieving reperfusion in infarct related artery to salvage myocardium, improve remodeling, electrical stability, potential to provide collaterals in the event of reinfarction in other territory, preserving left ventricular function and reduce mortality.

Landmark studies including GUSTO-1 and ISIS-2 have shown convincing benefits of thrombolysis and provide groundwork for current therapeutic practice. A review by Fibrinolytic Therapy Trialists' (FTT) Group has shown that thrombolysis prevents 20 – 30 deaths per 1000 patients with 25% reduction in mortality (Fibrinolytic Therapy Trialists (FTT) Collaborative Group, 1994). However 90 minutes arterial patency rate after streptokinase is only achieved in 50 – 60% and TIMI-3 flow from angiographic study is only achieved in 30% of patients (GUSTO investigators, 1993).

The open-artery hypothesis suggests that reestablishing a patent infarct related artery (IRA) with normal antegrade flow salvages stunned myocardial

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tissue, preserves left ventricular mechanical function and positively influences clinical outcomes including long term survival (Braunwald E, 1989). This hypothesis forms the basis for streptokinase use to achieve TIMI-3 flow in infarct -related artery.

Coronary angiography is the gold standard to determine artery patency after reperfusion but it is expensive, invasive and not always available early. Therefore bedside non-invasive markers are more attractive option. Among them, ECG criteria has good predictive value and sensitivity. It is also easily available and cheap. Other parameters used include resolution of chest pain and peaking of cardiac enzymes including troponin T, myoglobin and creatine kinase. However, chest pain resolution can be subjective since most patients would have received analgesic. Wherelse cardiac enzymes are not always available, results are often delayed and can be expensive causing difficulties in making decision for early alternative reperfusion strategies.

A paper by Sutton et al has shown that less than 50% resolution of ST segment elevation in the worst infarct lead had sensitivity of 81%, specificity of 88% and positive predictive value of 87% to predict less than TIMI-3 flow. ST elevation is measured 80 milliseconds after J point in ECG taken within 60-90min after given streptokinase (Sutton AGC et al., 2000).

Failure of thrombolysis with streptokinase is associated with factors including age, sex, race, location of myocardial infarction, "symptom-to-

needle" time, "door-to-needle" time, current smoking, diabetes, hypertension and high total white count (Conor FL et al., 1998).

My study aims to determine the failure rate of streptokinase as thrombolytic agent and its association with various independent variables as mentioned above. This may help us to predict earlier use of other reperfusion strategies including tPA, PTCA or CABG.

1.1 Thrombolytic Therapy

1.1.1 Physiology of thrombolysis

A blood clot or thrombus consists of blood cells occluded in a matrix of protein fibrin. Thrombolysis or fibrinolysis is enzyme-mediated dissolution of fibrin clot with plasmin, a trypsin-like serine protease. It is produced after proteolytic cleavage of inactive plasminogen in circulation mediated by various plasminogen activators e.g. tissue type (tPA) and urokinase type (uPA). The fibrinolytic activity is also modulated by inhibitors of plasminogen activators (e.g. plasminogen activator inhibitor-1 (PAI-1), a fast-acting inhibitor of tPA and uPA) and plasmin (e.g. alpha1-antiplasmin, alpha2-macroglobulin)

Recombinant forms of normal human plasminogen activators tPA and uPA are used in clinical intervention. Another commonly used agent is Streptokinase (sPA), a bacterial protein that does not occur naturally in human circulation. Their therapeutic action is via the activation of blood plasminogen to the clot dissolving plasmin. Unlike tPA or uPA, which are proteases, streptokinase possesses no enzymatic activity. Streptokinase acquires its plasminogen activating property by complexing with circulatory plasminogen or plasmin and the resulting high affinity 1:1 stoichiometric complex is a high-specificity protease that proteolytically activates other plasminogen molecules to plasmin (Castellino FJ, 1981).

Patients with non-ST elevation myocardial infarction and unstable angina do not benefit from thrombolysis. There are several reasons. Firstly, angiographic study has shown that the culprit artery is not occluded in 60-85%

of cases (TIMI IIIA investigators, 1993). Secondly, the non-occluding thrombus is platelet-rich which does not respond to thrombolytic therapy compared to AMI which is fibrin-rich. Lastly, microvascular perfusion is reduced in NSTEMI/UA and this is due to embolization rather than epicardial artery occlusion as in STEMI.

Patients with cardiogenic shock also respond poorly probably because of poor penetration of thrombolytic agent into occlusive thrombus and lack of adequate coronary perfusion pressure in setting of hypotension which is necessary to maintain vessel patency (Ijaz A. Khan and Ramesh M. Gowda, 2003).

1.1.2 Historical perspective

Before 1980, the management of patients with acute myocardial infarction was centered around pharmacologic therapy directed toward managing arrhythmias and attempting to limit the size of the evolving infarct. Although these efforts were partially effective, the morbidity and mortality from AMI remained high. Thrombolytic agents were first used for the treatment of acute myocardial infarct in 1958 and gained wide acceptance in 1980s after several prospective, randomized, controlled trials showed a clear mortality benefit (Ijaz AK et al, 2003).

Direct intracoronary administration of fibrinolysin was first reported from Russia in 1976 which subsequently led to reperfusion era that initially used intracoronary streptokinase in a few centers in the late 1970s and early 1980s

(Rentrop P and Blanke H, 1981). However initial therapy using intracoronary thrombolytic therapy was impractical as it required emergency coronary angiography and hence restricted to a few hospitals with facilities and trained personnel for coronary angiography. These problems subsequently led to the development of systemic administration of streptokinase for fibrinolysis.

The first landmark trial from Italy (Gruppo Italiano per lo Studio della Streptochinasi nell'infarto Miocardico (GISSI), 1986) has established the life-saving strategy of early intravenous thrombolytic therapy in acute myocardial infarction. US Food and Drug Administration (FDA) approval was granted in late 1987 following this study.

1.2 Comparing Plasminogen Activators

Different thrombolytic agent differs in their efficacy and fibrin selectivity. Even with the same thrombolytic agent, different doses, different administration regimens and concomitant use of adjunctive agents can cause significant variations to the patency rates (Ijaz A. Khan and Ramesh M. Gowda, 2003).

1.2.1 First generation agents

There are 3 agents in this group : streptokinase, urokinase and anisoylated plasminogen streptokinase activator complex (APSAC). These agents are not fibrin specific and they convert plasminogen to plasmin. There is a constant equilibrium between circulating plasminogen and plasminogen in the thrombus. Eventually there will be depletion of plasminogen which reduces clot lysis (known as "plasminogen steal"). Also both streptokinase and APSAC are immunogenic and can result in drug resistance, fever, hypotension and allergic reactions.

Urokinase is a two chain serine protease isolated from human kidney cells, so allergic effects are minimal. It has a half-life of 15-20 minutes and metabolized in the liver. Current interest is limited because, like streptokinase, it lacks fibrin specificity and like tPA, it is very expensive (3x of Streptokinase). In addition production is limited due to problems in manufacturing process. Anistreplase (APSAC) has longer half life than streptokinase so can be used as bolus but it is as antigenic as streptokinase with similar side-effects profile

and mortality benefits. Although the cost is higher, it does not have any compelling advantage. Hence it is not very commonly prescribed.

1.2.2 Second generation agents

Tissue plasminogen activator (tPA) or alteplase (Activase in United States and actilyse in Europe) is the most widely used fibrin selective agent in this group. It is a glycoprotein with 527 amino acids, produced using recombinant technology.

The risk of intracranial hemorrhage is higher than streptokinase (0.7 versus 0.5%). Other limitations include a procoagulant effect with resistance to recanalization in 15-40%. Only half reach TIMI 3 flow on angiographic study. Reocclusion rates may reach up to 10% at 1 week and 25% at 12 weeks and time to reperfusion delayed up to 45 minutes. Heparin is usually co-administered for at least 48 hours due to its short half-life and to avoid reocclusion. The accelerated dose regimen using not more than 100mg of tPA over 90minutes produces more rapid thrombolysis than the standard 3 hours infusion of tPA.

1.2.3 Third generation agents

They are derived from modifications of basic tPA structure and as a result, the half-life is lengthened. There is an increased resistance to plasma protease inhibitors and there is more selective binding to fibrin. Among these agents include reteplase, lanoteplase, tenecteplase and staphylokinase.

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Table 1.1 Characteristics of US-FDA Approved Thrombolytic Agents

Characteristics	STK	APSAC	Alteplase	Reteplase	TNKase
Molecular weight	47,000	131,000	70,000	39,000	70,000
Half life(min)	23	100	<5	13-16	20-24
Dose/time	1.5MU	30mg	100mg	10+10U	0.5mg/Kg
Bolus Adm	No	Yes	No	Yes	Yes
Metabolism	Hepatic	Hepatic	Hepatic	-	-
Allergic reaction	1-4%	-	<0.2%	No	<1%
Hypotension	Yes	Yes	No	No	No
Early Heparin	?Yes	?Yes	Yes	Yes	Yes
Fibrin Selective	No	No	Yes	Yes	Yes
Systemic Fibrinogen	Marked	Marked	Mild	Moderate	-
Fibrinogen breakdown	4+	-	1-2+	Unknown	4-15
Plasminogen binding	Indirect	Indirect	Direct	Direct	Direct
TIMI 3 flow (%)	32	43	54	60	66
90min patency (%)	50	65	75	80	75
Intracerebral bleed	0.5	0.6	0.8	0.9	-
Mortality rates(%)	7.3	10.5	7.2	7.5	

Abbreviations :

STK = Streptokinase

APSAC = Anistreplase

TNKase = Tenecteplase

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1.3 Streptokinase

Streptokinase is an extracellular enzyme produced by various strains of beta-hemolytic streptococci. It is a single-chain polypeptide with a molar mass of 47 kDa and made up of 414 amino acid residues. The protein exhibits its maximum activity at pH of 7.5 and it does not contain cysteine, cystine, phosphorus, conjugated carbohydrates and lipids (Banerjee A et al, 2004).

1.3.1 Structure and Mechanism of action

Different groups of streptococci produce streptokinase which differs in structural domains (i.e., alpha, beta, gamma) and functional properties. The exact mechanism on how streptokinase activates plasminogen remains to be elucidated. It is known that multiple domains are involved in interaction with plasminogen. The C-terminal of streptokinase is involved in plasminogen substrate recognition and activation and the Asp41 – His48 region is important in binding to plasminogen. The coiled region of streptokinase-gamma domain is said to be essential for plasminogen activation and similarly beta domain is involved in forming the streptokinase-plasminogen complex responsible for activating the plasminogen. The first 59 amino acid residues or N-terminal portion has important functional roles. Without the N-terminal, streptokinase has unstable secondary structures and thus reduces the activity of remaining amino acid residues (Banerjee et al, 2004).

1.3.2 Production of Streptokinase

Streptokinase producing streptococci were first identified in 1874 by Billroth in exudates of infected wounds. Later the blood of patients with scarlet fever

was shown to contain similar streptococci. In 1933, Lancefield used serologic distinctions to differentiate the beta-hemolytic streptococci into groups A to O. Most streptokinase was obtained from streptococci of Lancefield groups A, C and G. The group C is preferred as they lack erythrogenic toxins. The C strain of *Streptococcus equisimilis* H46A isolated from human source in 1945 has been widely used and it yielded the most active streptokinase. Subsequently, the streptokinase gene from *Streptococcus equisimilis* was sequenced by Malke et al (1985) and since then considerable information exists for effectively and safely producing recombinant streptokinase in non-pathogenic bacteria.

In order to produce streptokinase, streptococci need to grow and proliferate in suitable complex and rich media (known as fermentation). Since Bernheimer et al (1942), many modifications have been made on his original media in order to achieve high biomass growth. Christensen (1945) has used medium containing peptone, phosphate salts, glucose, biotin, riboflavin, tryptophan, glutamine and nucleic acids (thiamine, adenine and uracil) to produce streptokinase from *S.equisimilis* H46A. This medium contains less glutamine (25%) compared to Bernheimer's media and the low glucose content allow growth without generation of excessive acid. Continous culture has a higher productivity compared to batch culture. In addition batch culture has a rather extended lag phase followed by a short period of exponential growth.

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Other mediums used include Baewald et al (1975) containing yeast autolyzate or corn steep liquor as nitrogen source; brain-heart infusion (BHI) by Malke and Ferreti (1984) and Suh et al (1984); chemically defined media (CDM) which requires small inocula and comparable doubling time to complex media (McCoy et al 1991). Other methods include use of mutant *Streptococcus* and recombinant production which has far higher yield compared to culture method.

After fermentation, streptokinase must be assayed and quantified before they can be extracted. Assay of streptokinase rely on its ability to activate plasminogen (deriving from human, chimpanzee, monkey, cat, dog, and rabbit) to plasmin which then hydrolyzes an indicator substrate including fibrin clot, casein, other proteins and various synthetic esters (e.g. lysine methyl ester, lysine ethyl ester etc). Christensen (1949) devised the first quantitative method using fibrin clot as indicator substrate. Other methods include solid phase chromogenic assay for plasmin reported by Kulisek et al 1989; enzyme-linked immunosorbent assay (ELISA) for antibodies against streptokinase developed by Leornadi et al (1983) and enzyme immunoassay for streptokinase by Shemanova et al (1995). The latter method was more sensitive and requires only micro-quantities of blood serum.

The final step will be recovery and purification of streptokinase using various chromatography methods as described by De Renzo et al (1967), Tomar (1968), Taylor and Botts (1968), Einarsson et al (1979) and Perez et al (1998). Commercial production of streptokinase requires biosafety

consideration to process workers as the streptokinase protein can be immunogenic and streptococci can be potentially pathogenic.

1.3.3 Safety of thrombolysis

Bleeding (minor or major) is the major complication. However most bleeding is relatively minor. Most serious bleeding episodes occur in patients who undergo invasive procedures. Three quarters of bleeding episodes occur at vascular puncture sites (Sane DC and Califf RM, 1989). Intracranial hemorrhage is the most serious complication and its frequency depends on the regimen used and patient characteristics. It is more common with lanoteplase than with alteplase or tenecteplase and less frequent with streptokinase (Maggioni AP and Franzosi MG, 1992). The clinical variables known to predict increased risk of bleeding: patients over 65 years, female sex, low body weight (<70kg), hypertension on presentation and use of tPA compared to streptokinase.

There are reports of early mortality in the first 24 hours especially among elderly. The mechanism for early mortality include increased risk of myocardial rupture (especially elderly), fatal intracranial hemorrhage, and inadequate myocardial perfusion resulting in pump failure. However, excess mortality (10.5% of total deaths) is offset by the deaths prevented by thrombolysis (30 per 1000 patients presented within 6 hours) as shown in a meta-analysis (Fibrinolytic Therapy Trialists (FTT) Collaborative Group, 1994).

Previous exposure to streptococci in the past one year can produce antibody-mediated resistance to streptokinase and anistreplase in most cases. Other rare complications include splenic rupture, aortic dissection and cholesterol embolization.

1.3.4 Precautions and Contraindications

Preferably more than one peripheral venous access should be available and arterial punctures are avoided. Ideally procedures such as pulmonary artery catheters or temporary transvenous catheter placements, if needed, should be performed in an expeditious fashion prior to administration of thrombolytic agents. Subclavian catheter should be avoided because it is difficult to control any excessive bleeding.

Thrombolytic agents are considered as category C drugs in pregnancy. There are no animal studies and it is not known whether streptokinase can cause fetal harm when administered to the pregnant woman or whether it can affect reproduction capacity. It is also not known whether these agents are secreted in human milk (Ijaz AK et al, 2003).

Major recent streptococcal infection as mentioned above can cause resistance to streptokinase because of anti-streptococcal antibodies. Hypertension is a less contraindication against streptokinase than against alteplase. Gentamicin sensitivity is a specific exclusion criteria for use of alteplase (as gentamicin is used in the alteplase preparation).

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Table 1.2 : Contraindications for Fibrinolysis in ST-elevation Myocardial Infarct (Adapted from ACC/AHA guidelines 2004)

Absolute Contraindications	1. Any prior intracranial hemorrhage 2. Known structural cerebral vascular lesion 3. Known malignant intracranial neoplasm 4. Ischemic stroke within 3 months 5. Suspected aortic dissection 6. Active bleeding or bleeding diathesis including menstruation 7. Significant closed-head or facial trauma within 3 months
Relative Contraindications	1. History of chronic severe poorly controlled hypertension 2. SBP > 180mmHg or DBP > 110mmHg 3. History of prior ischemic stroke greater than 3 months, dementia or known pathology not covered above 4. Traumatic or prolonged (>10 minutes) CPR or major surgery less than 3 weeks 5. Recent (2 - 4 weeks) internal bleeding 6. Non-compressible vascular puncture 7. Pregnancy 8. Active peptic ulcer 9. Current use of anti-coagulants 10. Prior exposure or allergic reaction (more than 5 days) to streptokinase/anistreplase

1.4 Acute Myocardial Infarct

1.4.1 Definition

Acute myocardial infarction (AMI) is defined as necrosis of heart muscle due to inadequate blood supply following an acute coronary artery occlusion. This occlusion is usually due to plaque rupture or fissuring with superimposed thrombosis. Rarely this may result from coronary spasm, coronary embolism or vasculitis (Fallon JT, 1996).

1.4.2 Diagnosis

Diagnosis of acute myocardial infarct according to revised World Health Organization (WHO) definition in 1979 was based on the presence of at least two of the following three criteria (W.H.O., 1979):

1. Clinical history of ischemic type of chest discomfort
2. Evolutionary changes on serially obtained ECG tracings
3. A rise and fall in serum cardiac markers

However, this criteria has its limitations. Many patients who have STEMI are asymptomatic, a substantial number have an ECG with only nonspecific changes or may even be normal, and some patients have normal serum CK-MB but elevated troponins. Therefore these patients may be wrongly classified as unstable angina. As a result of these limitations, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) has proposed a new definition in year 2000 for acute, evolving or recent myocardial infarct. This new definition incorporated sensitive and specific

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markers including troponins and newer imaging techniques that are able to detect small infarcts that would not have considered AMI previously.

Either one of the following criteria would satisfy diagnosis of AMI (Alpert JS et al., 2000) :

1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following :

a. Ischemic symptoms

b. Development of pathological Q waves on ECG

c. ECG changes indicative of ischemia

d. Coronary artery intervention (e.g., coronary angioplasty)

Or

2. Pathological findings of an acute myocardial infarct

1.4.3 Chest Pain

Chest pain is the single most important symptom in AMI. It is usually retrosternal, usually lasts at least 20 minutes. It can occur at rest or with activity. The pain is usually central or in the left chest and may radiate to jaw or down the left upper limb. It may be crushing, pressing or burning in nature but severity of pain is variable. Occasionally the pain may occur in epigastric region and therefore may be misinterpreted as heartburn or indigestion.

Other associated symptoms include dyspnea, nausea and vomiting, palpitations, weakness, dizziness, lightheadedness and syncope. Diabetics, elderly and females may not present with typical ischemic type of chest pain.

In a local study, among 887 patients in Hospital Selayang; race, male sex, sudden onset of persistent crushing pain, associated with sweating and a history of diabetes mellitus were found to be significant predictors of AMI. Pain that is relieved by other means and history of heart disease on treatment are important predictors of a diagnosis other than AMI. The specificity is high at 80.5% (Bulgibaa AM and Razazb M, 2005).

Approximately two thirds of patients describe the new onset of angina or a change in their chest pain pattern in the month preceding infarction. However in approximately one fourth of patients, myocardial infarction is associated with only mild symptoms or no symptom of chest pain at all.

1.4.4 Electrocardiogram in diagnosis of AMI

Electrocardiogram (ECG) can demonstrate evolutionary changes of acute myocardial infarction starting from hyperacute changes of tall peaked T-wave which indicates localized hyperkalemia, ST segment elevation followed by Q-wave over several hours to days, return of ST segment to isoelectric baseline and T wave inversion.

Diagnosis of STEMI requires presence of ST segment elevation and pathological Q-waves. Criteria for ST segment elevation at J point are ≥ 0.2mV

in leads V1, V2 or V3 and ≥0.1mV in other leads and should be present in 2 or more contiguous leads. J point is described as the first turning point in ST segment.

Q-wave is the first negative deflection of QRS complex and it is pathological when duration is more than 0.04 seconds. Criteria for AMI would be presence of any Q-wave in leads V1-V3 or Q-wave greater than or equal to 30ms (0.03s) in leads I, II, aVL, aVF, V4-V6 and must be present in any 2 contiguous leads and be greater than or equal 1mm in depth (W.H.O., 1979).

Localization of infarct depends on the presence of both Q waves and ST elevation in certain contiguous leads. Anterior infarct has ECG changes over leads I, aVL and from V1 till V6. Inferior infarct has ECG changes over leads II, III and aVF. Right ventricular infarct has ECG changes over V4R and V5R.

If ST segment elevation is present along with typical chest pain, the likelihood that patient has acute myocardial infarct is greater than 90%. Other non-specific findings include ST segment depression, T wave inversion and bundle branch block but are less specific. Half of the patients with myocardial infarct may not have ST elevation.

1.4.5 Cardiac enzymes in diagnosis of AMI

Injury to cardiac myocytes will release intracellular enzymes into the blood allowing their detection. Traditionally creatinine kinase (CK) and its isoenzyme, creatinine kinase-myocardial band (CK-MB) were used as early

marker for diagnosis of acute myocardial infarct. Rapid assays were developed allowing faster availability of results within 30-60 minutes.

Drawbacks to its use include its lack of specificity for cardiac muscles and time required for CK-MB to rise. Both CK and CK-MB require at least 3 hours of profound ischemia in order to rise above normal. In addition, in patients who have only partial obstruction or presence of extensive collaterals can further delay the release of these enzymes.

In order to overcome these limitations, other blood tests were developed including myoglobin and troponins. Myoglobin is a low molecular weight heme protein in cardiac muscle and it is rapidly released from infarcted myocardium compared to CK-MB but it is also found in skeletal muscle making it less specific.

Troponin is a more specific marker, rises rapidly after infarction and has been proven in previous clinical trials to predict subsequent cardiac events. Since troponin is relatively new and expensive, it is not readily available in many coronary care units including our centre till recently.

1.5 Markers of Patency after Thrombolysis

1.5.1 Electrocardiogram criteria using ST segment resolution

Prognosis of AMI treated with thrombolysis is strongly related to achievement of early patency of culprit coronary artery and this was well documented in clinical trials in which coronary angiography has been performed shortly after thrombolytic therapy.

Various electrocardiogram markers have been proposed by various investigators as predictors of outcome but not all can adequately delineate risk strata for patients with AMI in the early hours after thrombolysis other than ST segment resolution. There are many criteria for ST segment resolution. Among them include ST segment reduction > 70%, 30 to 70% and less than 30%. Some investigators advocate criteria of less than 50% and some suggest complete resolution of ST segment as the most sensitive marker.

Review of few studies have shown that ST segment resolution of 50% correlates best with early patency after thrombolysis with good sensitivity and specificity. This is supported from papers by Sutton (2000) and Syed MA (2004) as described below.

In the study by Sutton (2000), which is a prospective cohort study conducted in a regional cardiothoracic unit involving 100 patients with acute myocardial infarct to determine whether simple, readily applicable ECG criteria will allow early prediction of inadequate (< TIMI 3) flow in the infarct related vessel in patients receiving thrombolytic treatment; and to determine

the success of streptokinase in achieving adequate antegrade flow in the infarct related vessel two hours after starting treatment. The ECG test that performed best among the six criteria was < 50% resolution of the ST segment elevation in the worst lead and no accelerated idioventricular rhythm. This had a sensitivity of 81%, specificity of 88%, positive predictive value of 87%, negative predictive value of 83%, and overall accuracy of 85%. (Sutton AGC et al., 2000)

Syed MA (2004) assessed the usefulness of a single lead ST resolution at 90 minutes after thrombolysis compared with the sum of ST resolution in predicting TIMI 3 flow, using prospectively collected data from the Limitation of Myocardial Injury Following Thrombolysis in Acute Myocardial Infarction (LIMIT-AMI) study. All patients had electrocardiogram recorded at presentation and 90 minutes and a coronary angiogram 90 minutes after thrombolysis. Infarct artery patency was assessed in 238 patients with 4 different ST resolution criteria: single lead ST resolution > or =50% and > or =70% and sum ST resolution > or =50% and > or =70%. The most sensitive criteria for TIMI grade 3 flow was single lead ST resolution > or =50% (sensitivity rate, 70%; specificity rate, 54%), whereas sum ST resolution > or =70% was most the specific criteria (sensitivity rate, 45%; specificity rate, 79%). The author proposed that single lead ST-resolution > or =50% as the optimal ECG indicator for successful reperfusion 90 minutes after thrombolysis (Syed MA et al., 2004).

In another study, the prognostic power of noninvasive markers of coronary artery reperfusion was evaluated in 967 patients with acute myocardial infarction who were treated with intravenous streptokinase. The following criteria were chosen : resolution of chest pain and ST-segment resolution >50% at 90 minutes, abrupt creatinine kinase rise before 12 hours, and T-wave inversion in infarct-related electrocardiographic leads within the first 24 hours after thrombolysis. Each reperfusion marker was associated with improved outcome but multivariate analysis showed that ST segment resolution was significantly and independently associated with low in-hospital mortality rate (Ramon C et al., 1999).

This classic and often quoted study by Schroeder (1995) has assessed prospectively the prognostic power of early ST segment resolution in a cohort of 1909 German patients in a substudy of The International Joint Efficacy Comparison of Thrombolytics (INJECT) trial which compared mortality in 6,010 patients randomized to receive either reteplase or streptokinase. The three groups of ST segment resolution were defined as complete (≥70%), partial (70% to 30%) and no resolution (<30% to >0%). Among 1,398 patients presenting <6 h, the 35 day mortality rate for complete, partial and no ST segment resolution was 2.5%, 4.3% and 17.5%, respectively (p < 0.0001). When baseline characteristics were included, no ST segment resolution was the most powerful independent predictor of 35-day mortality. The author concluded that partial ST segment resolution predicts larger infarct areas, but early mortality is relatively low (Schroeder R et al., 1995).

In another earlier report by Saran RK et al (1990), a reduction of greater than 25% in ST segment elevation 3 hours after thrombolytic treatment and angiographic study in 83 patients had a sensitivity of 97% but a specificity of only 43% in predicting a patent infarct artery or preservation of left ventricular function.

As a conclusion, newer trials using prospective design have shown that electrocardiogram criteria using ST segment resolution of < 50% is a sensitive early marker of patency after thrombolysis.

1.5.2 Other electrocardiogram markers of patency

Other investigators have attempted to evaluate other electrocardiogram markers but were thought to be too complex and too technical to be used in clinical practice. Some of these studies may be flawed in designs and others which could not demonstrate its superiority over ST segment resolution as early marker of patency.

Another potential marker would be T wave inversion in the infarct related ECG leads but it is limited by its late occurrence after 24 hours. For example, (Matetzky S et al., 1994) found that T wave inversion was associated with TIMI III flow in a series of 100 patients after thrombolysis within 36 – 48hours. Similarly, (Castro P et al., 1992) has compared T wave inversion with other reperfusion indexes and found that it was the most significant predictor of patency after thrombolysis at 24 hours.