

## Coronary Thrombolysis: Suggestions For Pakistan

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The pathogenesis of myocardial infarction has long been subject of debate. There is now strong evidence that myocardial infarctions caused by coronary thrombosis, some of these occlusions' being rather temporary while most are permanent. It has been shown that the quantity of myocardium lost is less if the coronary occlusion is relieved early. Acute coronary thrombolysis in the management of myocardial infarction was first described over 28 years ago (Fletcher et al, 1959). Despite early encouraging results, it fell into disrepute because of frequent bleeding complications. Recent renewed interest in this treatment has followed angiographic demonstration of thrombotic occlusion of infarct related coronary artery in upto 90% patients with acute myocardial infarction, when studied within 4 hours of onset of symptoms (1). The aim of coronary thrombolysis is to limit the size of myocardial infarction, preserve left ventricular function and improve prognosis by dissolving the thrombus causing the acute coronary occlusion.

In Pakistan with the high incidence of coronary artery disease, coronary thrombolysis has much to offer in early management of myocardial infarction. The benefits of coronary thrombolysis depend on the speed of initiation of therapy after the onset of symptoms. The difficulty of rapid access for the population as a whole to hospital based acute medical services is a problem. However, for the urban population access to emergency departments is easier. Early presentation will be greatly enhanced by education of the population to recognise the symptoms of acute myocardial ischaemia or infarction. There should also be an increased emphasis on more rapid attention from the medical staff to patients presenting with chest pain.

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### SELECTION OF PATIENTS FOR THROMBOLYSIS

Patient selection criteria should be simple and clearly defined (Table-1). Thrombolytic therapy should be offered to patients presenting within 12 hours of onset of typical symptoms of myocardial infarction. In our context, the time window for administration of coronary thrombolysis should be kept wide so as to overcome the difficulties of rapid access to hospital. Although the benefits of thrombolytic therapy diminish with time after the onset of symptoms, there is ample evidence from large multicentre studies (2,3) that benefits of mortality reduction and myocardial salvage are present even when thrombolysis is administered as late as 12 hours after the onset of symptoms. This should not however undermine the importance of early administration of this treatment.

1	Age less than 70 years.
2	Ischaemic chest pain accompanied by ST segment elevation of 1 mm or more in any limb lead and/or 2 mm or more in any precordial lead.
3	Patient admitted within 12 hours of onset of symptoms.

Table-1: Patient selection criteria

Apart from typical symptoms, suitable patients should demonstrate ST segment elevation in ECG as indicated in Table-1. This is a safeguard against giving thrombolytic treatment to patients without myocardial infarction and more importantly to patients with conditions that contra indicate thrombolysis, e.g., aortic dissection, perforated peptic ulcer, pericarditis etc.

Other contra indications to thrombolysis are shown in Table-2. Effective thrombolysis is particularly important in patients with anterior infarction.

1	Active or recently symptomatic peptic ulceration.
2	Cerebrovascular disease.
3	Current anticoagulant therapy.
4	Bleeding diathesis.
5	Systemic hypertension.
6	Recent surgery / trauma.
7	Cardiopulmonary resuscitation.
8	Diabetic retinopathy.
9	Menstruating / pregnant females.

**Table-2: General contraindication to thrombolysis**

#### Expanding Indications:

There is as yet no multicentre trial proof of the benefits of coronary thrombolysis in patients with previous myocardial infarction. ST segment depression on ECG with typical symptoms or in patients with unstable angina, but on first principles these groups with pre-existing reduced myocardial reserve should benefit.

#### CHOICE OF THROMBOLYTIC AGENT AND ROUTE OF ADMINISTRATION

Drugs which can be used for coronary thrombolysis include streptokinase, urokinase and recombinant tissue type plasminogen activator (T.P.A.). These agents have been extensively investigated in large trials, while others like acylated plasminogen streptokinase activator complex (APSAC) are currently being evaluated. On the whole, there are small differences in the thrombolytic efficacy when used within 3 hours of onset of symptoms (4-8). However with delayed administration (between 6 and 12 hours of onset of symptoms) TPA has been shown to produce higher reperfusion rates up to 75% (9) as compared with 55 - 65% with streptokinase (10). TPA has been promoted as being clot specific; this property is relative and it does produce a systemic lytic state which is comparable to that produced with less thrombus selective

agents (11). The incidence of bleeding complications is about the same with all the thrombolytic agents when administered to carefully selected patients. None of them affords safety against haemorrhagic complications.

With our financial constraints in health care and the huge costs of providing thrombolytic therapy in acute myocardial infarction, streptokinase would be the agent of choice. It is the most extensively investigated agent showing consistent reperfusion rates of 55-65% and is least expensive. Cost per patient treatment is 1/10 of that with TPA and 1/5 of that with APSAC. There is a trade off with risk of hypersensitivity reactions with streptokinase but these have not been a major problem in large multi-centre studies. Although thrombolytic agents can be administered via both intracoronary and intravenous routes, (with higher reperfusion rates with the former route), intravenous route would be of choice in Pakistan.

#### Complications:

The commonly encountered complications of coronary thrombolysis are bleeding, reperfusion arrhythmias and hypersensitivity reactions. As expected the majority are haemorrhagic; these are usually minor and can be controlled with discontinuation of lytic therapy and rarely a severe haemorrhage requires blood transfusion. These complications can be minimised by careful selection of patients. Reperfusion arrhythmias are rarely a management problem. The commonest are idioventricular rhythms and frequent premature ventricular contractions. Sinus bradycardia and A.V. block are sometimes seen on reperfusion on inferoposterior myocardium. Hypotension is occasionally seen during the infusion of a thrombolytic agent.

One complication peculiar to streptokinase is hypersensitivity reactions. As it is derived from streptococci, hypersensitivity to streptococcal antigen can develop and crosssensitization may occur. The allergic manifestations are usually minor, e.g., skin rash, fever, shivering, nausea and vomiting. Anaphylatic shock, serum sickness like syndrome and deterioration of renal function are rare but potentially important hypersensitivity reactions. Premedications with hydro-

cortisone reduces the chances of these hypersensitivity reactions.

#### Clinical Markers of Reperfusion :

None of the noninvasive markers of reperfusion are accurate predictors of recanalization status of the infarct-related coronary artery. Reduction of chest pain, improvement of ST elevation on the ECG and reperfusion arrhythmias are usually taken as clinical indicators of reperfusion. None of these is an independent predictor of recanalization status, but concordance of all these three criteria, when present accurately predicts recanalization.

#### MANAGEMENT OF PATIENTS AFTER THROMBOLYSIS

##### Early Management :

After completion of thrombolytic therapy anticoagulation with heparin is used to maintain the benefits of thrombolysis. This is particular important with agents with a short plasma half like TPA where higher rethrombosis rates have been reported (7) compared with streptokinase and APSAC which have longer plasma half life. In the GISSI study using streptokinase, anticoagulation was not part of the protocol and there have been reports of higher incidence of early reocclusion and reinfarction. In ISIS-2 study reported recently, use of aspirin following thrombolysis was found to have an additive beneficial effect on mortality reduction, presumably through reduced reocclusion rates. In Pakistan, aspirin would be a more attractive option than heparin and would reduce the overall costs of thrombolysis.

##### Late Management:

A definitive post thrombolysis strategy should be devised in addition to medical treatment. After successful reperfusion of ischaemic myocardium, the patients is left with a patent infarct-related artery with a critical stenosis. Clearly this unstable plaque may attract rethrombosis and cause reinfarction. Under ideal circumstances coronary angiography would be the next step, but a submaximal pre-discharge exercise test would be helpful to screen the patients at risk of reinfarction in the salvaged myocardium.

Early reoccurrence of angina or demonstration of inducible ischaemia in the territory of aborted infarction would indicate need for early coronary angiography. The subsequent management (aorto coronary bypass grafting, angioplasty or continued medication) should be based on angiographic findings.

#### CONCLUSIONS

1. Thrombolytic therapy can be safely administered to patients with acute myocardial infarction in a district general hospital.
2. In order to expedite the arrival of patient in the emergency department and early institution of thrombolytic therapy, health education of general population to recognise symptoms of myocardial ischaemia should be a priority.
3. It is important to emphasis to the general practitioners and hospital doctors in particular the importance of early thrombolytic treatment as part of the management of acute myocardial infarction management.

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