CORONARY THROMBOLYSIS A PAKISTANI PERSPECTIVE

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The pathogenesis of myocardial infarction has long been subject of debate. There is now strong evidence that myocardial infarction . is caused by occlusion of a coronary artery by a thrombus at the site of a ruptured atheromatous plaque[1]. Some of these occlusions are temporary while most are permanent. It has been shown that the quantity of myocardium lost is less if the occlusion is relieved early[2]. Acute coronary thrombolysis in the management of myocardial infarction was described in late 1950s and early 1960s after pioneering work on this subject using open chested anaesthetised dogs to study the effects of reperfusion on ischaemic myocardium[3]. 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[4]. The aim of coronary thrombolysis is to limit the size of myocardial infarction, preserve left ventricular function and improve short and long term 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 the early management of myocardial infarction. â€˜The benefits of coronary thrombolysis depend on the early 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 relatively easy. Early presentation can 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.

Selection of patients for thrombolysis

Thrombolytic therapy should be offered to patients presenting within 12 hours of onset of typical symptoms ofmyocardial infarction. In our context, the time window for administration of thrombolysis should be kept wide so as to overcome 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 multicentre studies[5-7] that benefits of mortality reduction and myocardial salvage are statistically significant 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 in the critical first few hours after infarction. Apart from typical symptoms, suitable patients should demonstrate ST segment elevation in the ECG as indicated in Table 1.

TABLE I. Patient selection Criteria.

1	Age less 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 praecordial lead.
3	Patient presenting within 12 hours of onset of symptoms.

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 II.

TABLE II. Specific Contraindications to Thrombolysis.

1	Active or recently symptomatic peptic ulceration.
2	Cerebrovascular disease, e.g., previous stroke.
3	Current anticoagulant therapy.
4	Bleeding diathesis.
5	Uncontrolled systemic hypertension e.g above 160/110.
6	Recent surgery or trauma.
7	Cardiopulmonary resuscitation.
8	Proliferative diabetic retinopathy.
9	Women during menstruation or pregnancy.

Effective thrombolysis is particularly effective for salvaging myocardium in patients with anterior myocardial infarction2,5. Other patient selection criteria are given in Table 1.

Expanding indications

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

Choice of thrombolytic agent and route of administration

Drugs which have been used for coronary thrombolysis are streptokinase, urokinase recombinant tissue type plasminogen activator (T.P.A.) and acylated plasminogen streptokinase activator complex (APSAC). In large multicentre trials these agents have been extensively evaluated[5-9]. On the whole, there are small differences in their thrombolytic efficacy when used within 3 hours of onset of symptoms[5-13]. However, with delayed administration (between 6 to 12 hours of onset of symptoms) TPA has been shown to produce higher reperfusion rates of upto 75%[13] as compared to 55% to 65% with streptokinase[10,14,17] TPA has been promoted as clot specific agent but this property is relative and it does produce systemic lytic state which is comparable to that produced with less thrombus selective agents[15]. The incidence of bleeding complications is about the same with all the thrombolytic agents when administered to carefully selected patients. None of the thrombolytic agent affords safety against haemorrhagic complicaIn Pakistan, with our financial constraints in health care and huge costs of providing thrombolytic therapy in acute myocardial infarction streptokinase should be the agent of choice. It is the most extensively investigated agent showing consistent reperfusion rates of 55-65% and is the least expensive of the group of drugs. The cost of treatment is 1/10 of that of TPA and 1/5 of that of APSAC. There is however, a greater risk of hypersensitivity reactions with streptokinase but these have not been a major problem in large multicentre studies[5-8]. Thrombolytic agents can be administered via both intra coronary and intravenous routes. Although higher reperfusion rates have been reported with the intracoronary route[16], intravenous administration would be of choice in Pakistan. Intravenous administration of thrombolysis also facilitates early institution of therapy. The recommended regimen for intravenous streptokinase is the most widely practiced one, as suggested by Schroder et al[18], 1.5 million units of streptokinase given by slow intravenous infusion over 60 minutes.

Complications

The commonly encountered complications of coronary thrombolysis are bleeding, reperfusion arrhythmias and hypersensitivity reactions[5,16]. Haemorrhage is usually minor and can be controlled by discontinuation of lytic therapy. Rarely severe haemorrhage occurs and haemostasis can be achieved by blood transfusion. Reperfusion arrhythmias are rarely a problem in the management. The commonest are idioventricular rhythm and frequent premature ventricular contractions. Sinus bradycardia and A.V. block are sometimes seen on reperfusion of inferoposterior myocardium. Hypotension is occasionally seen during infusion of athrombolytic agent, particularly with streptokinase. One complication peculiar to streptokinase is hypersensitivity reaction. As streptokinase is derived from streptococci, hypersensitivity to streptococcal antigens can develop with streptococcal infections and cross sensitization may occur on administration of streptokinase. These allergic manifestations are usually minor, e.g., erythematous or urticarial skin rashes, fever, shivering, nausea and vomiting. Rarely anaphylactic shock, serum sickness like syndrome and deterioration of renal function occur which are potentially life threatening[5-7]. Premedication with parentral steroids probably helps in reducing the chances of these reactions. In patients who are candidates for second thrombolytic treatment within six months of thrombolysis with streptokinase, repeat use of this agent is contraindicated. This is because of a very high risk of anaphylaxis and potential lack of therapeutic efficacy in presence of high titres of specific antibodies resulting from the first exposure to streptokinase. In this scenario, tissue plasminogen activator would be the agent of choice.

Clinical markets of reperfusion

The non-invasive markers of reperfusion like reduction of chest pain, improvement in ST segment elevation on ECG and reperfusion arrhythmias individually are not accurate predictors of recanalization status of the infarct - related coronary artery[7]. A concordance of all these three criteria, when present, accurately predicts recanalization.

Management of patients after thrombolysisearly management

After completion of thrombolytic therapy anticoagulation with intravenous heparin is used to prevent recurrent thrombosis and maintain the benefits of thrombolysis. This is particularly important with agents with short plasma half life like TPA where higher rethrombosis rates have been reported[11] compared with streptokinase and APSAC which have longer plasma half life. In GISSI study[5] using streptokinase, anticoagulation was not part of the protocol and there were reports of higher incidence of early reocclusion and re-infarction. In ISIS-2 study[6], use of aspirin following thrombolysis was found to have additive beneficial effect on mortality reduction and preservation of left ventricular function, presumably through reduced reocclusion rates. In this study additional beneficial effect of aspirin administration with coronary thrombolysis and intravenous heparin have also been reported. In Pakistan, aspirin would be a more attractive option than heparin infusion because of ease Of administration and reduction in overall costs of thrombolysis.

Late management

A definitive post-thrombolysis strategy should be reperfusion of ischaemic myocardium the patient is left with devised in addition to medical treatment. After successful a patent infarct - related coronary artery with a critical stenosis. The unstable plaque at the site of occlusion may attract rethrombosis and cause re-infraction. Under ideal circumstances, coronary angiography would be the next step, but a sub-maximal predischarge exercise test would be helpful to screen the patients at a higher risk of reinfarction in the salvaged myocardium. Early recurrence of angina or demonstration of inducible ischaemia in the territory of aborted infarction would indicate the need for early coronary angiography. The subsequent management (aorta - coronary bypass grafting, angioplasty or continued medication) should be based on angiographic findings.

Conclusion

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

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