

CHAPTER

70

Thrombolysis in Acute Myocardial Infarction

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Introduction

Reperfusion of the occluded coronary artery at the earliest is the most important aim of management of STEMI. Once a flow is established, to aim at TIMI III (maximum flow without obstruction) flow is equally important. Leaving aside a small percentage of relief of coronary artery spasm and spontaneous recanalization, most patients need either PCI or IV thrombolysis to achieve reperfusion. Direct angioplasty in STEMI (PAMI) has shown major advantages over IV thrombolysis. Yet, especially in Indian conditions, IV thrombolysis, is the cornerstone of initial treatment choice because of the ease of administration, cost involved and feasibility issues. With the availability of third generation single push thrombolytics, role of IV thrombolytic should be redefined.

Thrombolytic agents

Starting with streptokinase (STK), various thrombolytics are available. Tenecteplase (TNK) is today the widest used thrombolytic in USA.¹ STK is still the most used & cost effective agent in developed country. Urokinase (UK) has been used mainly in Southeast Asia with adequate results but the experience is not large enough and authentic enough to be translated into routine practice. TNK is the agent of choice for pre-hospital thrombolysis. (Table 1)

All the thrombolytics should be used according to the current AHA/ACC guidelines.

Use IV thrombolysis in

- Where PAMI facilities are not available.
- Within first three hours of ST elevation.²
- Where PAMI is not available in the 90 minutes of contact with the patient and IV thrombolysis can be administered.
- Upto 24 hours of pain if ST changes & symptoms indicate ongoing ischemia & if PCI is not feasible.

Current guidelines for use of thrombolytics in acute MI, American College of Cardiology/American Heart Association

Class I

- In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptoms onset within the prior 12 hours and ST-segment elevation. > 0.1 mV in at least two contiguous precordial leads or at least two adjacent limb leads (Level of evidence: A).
- In the absence of contraindications, fibrinolytic therapy should be administered to STEMI

Table 1

	Streptokinase	Alteplase	Reteplase	Tenecteplase
Immunogenic	Yes	No	No	No
Administration	Infusion	Infusion	Two bolus doses 30 min apart	Bolus
Time required for complete dosing	60 minutes	90 minutes	30 minutes	5 seconds
Fibrin specificity	-	++	+	+++
Inhibition by PAI-I	?	Yes	?	80 times less susceptible than alteplase
Weight adjusted dosing	No	No	No	Yes
30 day mortality (%)	~7.5	6.1	~7.5	6.1

patients with symptom onset within the prior 12 hours and new or presumably new left bundle branch block 9 level of evidence: A).

Class IIa

- In the absence of contraindications, it is reasonable to administer fibrinolytic therapy to STEMI patients with symptom onset within the prior 12 hours and 12-lead electrocardiography findings consistent with a true posterior MI (level of evidence: C).
- In the absence of contraindications, it is reasonable to administer fibrinolytic therapy to patients with symptoms of STEMI beginning within the prior 12 to 24 hours who have continuing ischemic symptoms and ST elevation greater than 0.1 mV in at least two contiguous precordial leads or at least two adjacent limb levels (level of evidence: B).

Class III

- Fibrinolytic therapy should not be administered to asymptomatic patients whose initial symptoms of STEMI began more than 24 hours earlier (level of evidence: C).
- Fibrinolytic therapy should not be administered to patients whose 12-lead ECG shows only ST-segment depression, except if a true posterior MI is suspected (level of evidence: A).³

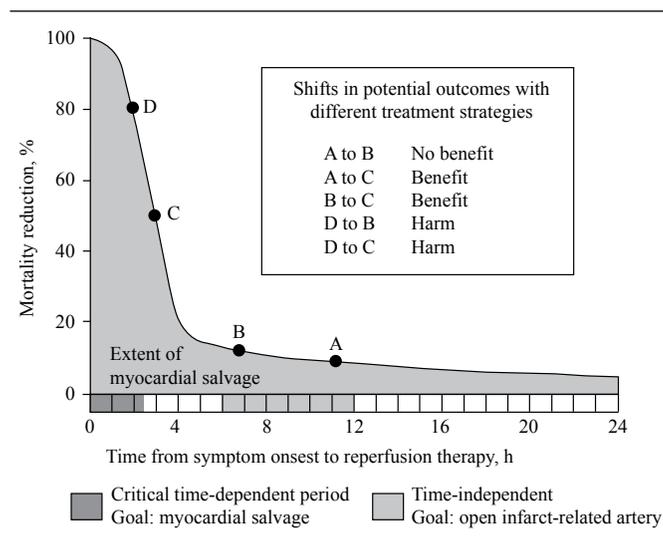
Contraindications and cautions for fibrinolysis in STEMI

Absolute contraindications to thrombolysis

- Any prior ICH.
- Known structural cerebrovascular lesion (e.g., arteriovenous malformation).
- Ischemic stroke within 3 months except acute ischemic stroke within 3 hours.
- Suspected aortic dissection.
- Active bleeding or bleeding diathesis (except menses).

Relative contraindications to thrombolysis:

- History of chronic, severe, poorly controlled hypertension.
- Severe uncontrolled hypertension on presentation (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg).
- Traumatic or prolonged (> 10 min) cardiopulmonary resuscitation or major surgery (within < 3 weeks).
- Recent (within 2 to 4 weeks) internal bleeding.
- No compressible vascular punctures.
- For streptokinase/anistreplase; prior exposure (> 5 days) or prior allergic reaction to these agents.

Figure 1: Thrombolysis in acute myocardial infarction

- Pregnancy.
- Active peptic ulcer.

History of prior ischemic stroke (> 3 months), dementia, or known intracranial pathology not covered in absolute contraindications. Current use of anticoagulants: the higher the INR, the higher the risk of bleeding.³

PAMI versus IV thrombolysis

Given a choice, PAMI is superior to IV thrombolysis especially after 3 hours of ST elevation. Because of various feasibility issues, if the door to balloon time is more than 90 minutes, it is worthwhile thrombolysing the patient. In the first 3 hours, reperfusion for salvage of myocardium is the aim therefore the therapy that can be offered earlier should be selected. Delay in therapy in this “steep” portion, can harm the patient (Fig 1). Shift from D to C/B/A is harmful. Shift to A to B is neutral. Shift from A to C/D is useful. In short, if PAMI is going to be delayed by 90 minutes, choose IV thrombolysis.

Effects of IV thrombolysis

Within 12 hours, successful recanalization with STK has 18% relative risk reduction at 30 days.⁴ All trials with successful recanalization with various agents show reduction in mortality. The success rate

with all thrombolytics is upto 70%. 50% patients achieved TIMI III flow & 20% achieved TIMI II flow. Allergic reactions, fever, hypotension are common with STK but the newer agents hardly show such effects. The rate of major bleed requiring transfusion is about 1-2% in all trials.⁵

Adjuvant therapy for IV thrombolysis on admission

- Aspirin : 150 mg or more of soluble aspirin.
 - Clopidogrel : 75 mg daily without a loading dose.⁶
 - LMWH : 30 mg IV Enoxaparine if TNK is used.¹
 - UFH : 5000 IV bolus followed by infusion if TPA is used.
- After thrombolysis is over, aspirin, clopidogrel need to continue. Enoxaparine/Raviparine should be used subcutaneously for 7 days.
- Direct thrombin inhibitors (Hirudin, Bivalirudin) has shown less re-infarction at 30 days but at increased risk of adverse bleedings.⁷
 - NSAID are contraindicated.

Use of Glycoprotein IIb/IIIa inhibitors in STEMI

Use of abciximab with thrombolytics led to increased TIMI III flow, did not address mortality benefit and had higher major bleeding & complications.^{7,8} Half dose lytics & abciximab reduced ischemic events but without mortality benefits.² Incidence of bleeding increased. Use of tirofiban & eptifibatide is too small to be quoted but trials were given up for increased bleeding. In a small pilot study of eptifibatide, it was used for failed thrombolysis but no proven literature is available. Many Indian clinicians use tirofiban for STEMI as “transfer” treatment but this practice is observational and not backed by evidence. The bottom line is GP IIb-IIIa inhibitors are out of bounds for use in STEMI either as “facilitation” or an adjuvant to or as post IV thrombolysis treatment.

Failed thrombolysis

Success rate of IV thrombolysis is close to 70%. Therefore strategies for failed thrombolysis or reocclusion/reinfarction also need to be planned in advance. Ongoing pain, non-resolution of ECG, hemodynamic or electrical instability indicate failure of recanalization. Repeat thrombolysis with the same or other agent is not to be practiced. A rescue PTCA must be encouraged even though the outcomes of rescue PTCA are not good. If rescue PTCA is not available small molecule GP IIb-IIIa inhibitors, tirofiban, eptifibatide can be used as a 24 to 48 hour infusion as a last resort.

Pre-hospital thrombolysis

Importance of “early” thrombolysis cannot be over emphasized. Transfer times to tertiary hospital even in cardiac ambulances can be long. Thrombolytics like STK, TPA need continuous infusions & monitoring. Considering all of the above, TNK single dose push in pre-hospital setting like general practitioners clinic, casualties of corporate hospitals, home & ambulances need to be considered. Large mortality & morbidity benefits have been shown in pre-hospital thrombolysis.¹⁰ Telemedicine for E-transfer of ECG could be a vital aspect of this treatment. Medical insurance to all, removing the obstacle of cost of thrombolysis will be an additional help. In general, by using modern amenities, modern thrombolytics and scientific advances an all out effort to increase pre-hospital thrombolysis should be made.¹¹

Future of IV thrombolysis

Pre-hospital thrombolysis after making a quick decision will be the order of the day. Such a thrombolysed patient may then be transferred to a tertiary centre with an acceptable delay. Lanoteplase, Saruplase (Rescupace), Staphylokinase are recombinant products of existing thrombolytics.¹² These products are in trial phase & may or may not prove to be improvements on the latest player – tenecteplase. Oral thrombolytic is a dream, which

is unlikely to replace IV thrombolysis in the near future.

IV thrombolysis in reference to Indian settings

It is now widely accepted that early IV thrombolysis (pre-hospital included) can be highly effective treatment.¹² In India where primary angioplasty can be offered to a small portion of patients within few hours of chest pain due to various feasibility issues, IV thrombolysis is even more important. Small hospitals, rural centers and other areas where patients reach first should be considered “pre-hospital” environments while a transfer is organized. A growing number of “young” AMI patients is a population yet not presented in evidence. This population of under forty, first MI, contain mainly thrombus in the occluded coronary artery. Subjecting these for primary stenting would mean a foreign body in a young person for no reason. These individuals respond dramatically to early and effective thrombolysis.

The common errors made in practice of IV thrombolysis should be avoided and following points need to be pondered.

- Aim as earliest thrombolysis unless it is already six hours old.¹³
- Use full dose STK in 30 minutes infusion (Please check expiry date and standard of the STK company).
- Avoid use of Urokinase as thrombolytic for AMI.
- Shift towards use of tPA and TNK should be made.
- “Pre-hospital” use of TNK should be the order of the day.

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