Thrombolysis in the Era of Intervention

SS Iyengar†, Girish S Godbole‡

Abstract

Thrombolysis revolutionized the treatment of acute ST – elevation myocardial infarction in the latter part of the last century and has been in use for more than two decades. Use of thrombolytic therapy is widespread owing to its safety, efficacy, ease of use, and affordability. Thrombolytic therapy has several limitations, many of which have been overcome with the adoption of percutaneous coronary intervention techniques in recent years. Primary percutaneous intervention is currently the preferred form of reperfusion therapy in the management of ST elevation myocardial infarction. However, thrombolytic therapy continues to have a role in many situations even in this era of intervention.

Introduction

“A short distance from its origin, the left coronary artery was completely obstructed by a red thrombus that had formed at a point of great narrowing… The hope for the damaged myocardium lies in the direction of securing a supply of blood”

- James B Herrick. 1912

Acute myocardial infarction is usually due to disruption of an atherosclerotic plaque in a coronary artery followed by thrombus formation. The complete occlusion of the lumen of a major epicardial coronary artery leads to acute ST – Elevation Myocardial Infarction (STEMI). Prompt, complete and sustained restoration of antegrade flow in the infarct related artery is essential to salvage the myocardium at risk, improve ventricular function and reduce short term morbidity and mortality.

There are two methods of achieving reperfusion of the myocardium at risk in acute STEMI. It is either by pharmacological therapy by using thrombolytic agents or by mechanical means by way of primary percutaneous coronary intervention (Primary PCI). Primary PCI has proved to be the superior, and therefore preferred, reperfusion strategy. Based on evidence, all major scientific organizations in their guidelines recommend Primary PCI as the reperfusion therapy of first choice for the management of acute STEMI. Consequently, the number of patients worldwide that receive Primary PCI for STEMI has been steadily increasing. However, Primary PCI has major logistic limitations of availability, accessibility and affordability.

Primary PCI for the treatment of acute STEMI in India is being practiced in several centers. However, availability of this treatment has been largely urban-centric and limited to the affordable and the insured. Thrombolytic therapy continues to be the most commonly used management strategy for acute STEMI in our country and, indeed, in most parts of the world.

Thrombolytic therapy is beneficial

Since the time of De Wood and colleagues who convincingly established the prevalence of total thrombotic coronary occlusion during the early hours of acute trans-mural myocardial infarction, reperfusion therapy has evolved, over the years, from intra-coronary thrombolysis to intravenous thrombolysis and now to mechanical reperfusion.

It was the Italian study in 1986 that established streptokinase as an effective thrombolytic agent when used intravenously. Thrombolytic therapy using streptokinase rapidly became the preferred strategy for the management of acute myocardial infarction. Many new thrombolytic agents were developed in due course to overcome some of the limitations of streptokinase like antigenicity, allergic reactions and systemic fibrinogen depletion. These newer thrombolytic agents could be administered as a bolus as opposed to Streptokinase which needs to be administered as an infusion.

Thrombolytic Agents

Streptokinase: This was the first thrombolytic to be used in the management of STEMI, initially by the intracoronary route and subsequently as an intravenous infusion. Streptokinase is isolated from bacteria and hence is antigenic. It should not be reused in any patient for a second STEMI, since pre – formed antibodies can neutralize the standard doses of streptokinase. Therefore, repeat thrombolysis, when required, should be carried out using a non - immunogenic agent.

Tissue Plasminogen Activator (t-PA, alteplase): It is a non - antigenic, second generation thrombolytic and produces only mild systemic fibrinogen depletion. t-PA is administered in an accelerated dose regimen over 90 minutes. Modification of t-PA has led to the development of third generation thrombolytic agents like reteplase and tenecteplase, which have prolonged plasma clearance and could therefore be administered as a bolus.

Reteplase: It is are combinant mutant form of t-PA. The GUSTO-III trial, which compared reteplase with t-PA in 15059 patients, did not demonstrate superiority of reteplase over or equivalence with t-PA. However, many experts consider these two agents to be equivalent, and reteplase has the advantage of a ‘double bolus’ administration (10 + 10 units).

Tenecteplase: It is a third generation thrombolytic, a mutant of t-PA, modified in such a way that it has decreased plasma clearance, increased fibrin specificity and reduced sensitivity to plasminogen activator inhibitor-1. ASSENT 2 compared single bolus tenecteplase with accelerated dose t-PA in 16,949 patients of STEMI. Tenecteplase proved to be equivalent to t-PA with respect to 30 day mortality and major bleeding. However, in patients who were treated after 4 hours of onset of symptoms, mortality rate was significantly less with tenecteplase as compared to t-PA (7.0 % with tenecteplase versus 9.2 % with t-PA, p = 0.018).

With the introduction of an indigenous preparation of tenecteplase in India, a number of Indian studies have established the safety and efficacy of tenecteplase in the treatment of Indian patients with STEMI.
The Evidence for Thrombolytic therapy

When administered in appropriately selected patients early after the onset of acute STEMI, the benefits of thrombolytic therapy have been established beyond doubt. FTT collaborative study13 included in their analysis all trials that randomized at least 1000 patients of suspected MI. In all, 9 trials and 58,600 patients formed the study material. Major adverse events during hospitalization and deaths during the first five weeks after MI were analysed. Though there was an excess of death during days 0 - 1, especially amongst the elderly and those presenting after 12 hours, there was an abundantly clear overall benefit outweighing the “early hazard”. The benefit was evident in patients with ST elevation and those with new – onset LBBB, irrespective of age, gender, blood pressure, heart rate, prior MI and diabetes. The absolute mortality reduction was 30 per 1000 patients presenting within 0 - 6 hours and 20 per 1000 patients presenting between 7 and 12 hours. Beyond 12 hours, the benefit was uncertain. So, the earlier the treatment is administered, greater is the benefit.

Alteplase is more fibrin-specific and non-antigenic, and mortality with accelerated infusion of alteplase was less when compared with streptokinase. Retepase has ease of administration, but has no additional advantage over alteplase.9 Tenecteplase, which can be given as a single intravenous bolus was equivalent to accelerated t-PA and had significantly lower rate of non - cerebral hemorrhage.10 Tenecteplase was superior to t-PA in a subgroup of patients who were treated after a time window of 4 hours, mortality rate being 7.0% vs 9.2% in favour of tenecteplase.

In an observational registry from India,12 data of 6000 patients of STEMI receiving tenecteplase showed that thrombolysis was successful in 90.9%, the overall in-hospital mortality was 3.2% and the incidence of intracranial hemorrhage was 0.62%.

The earlier the thrombolytic therapy is administered, the more beneficial is the therapy. A meta - analysis of 22 studies showed a substantially larger mortality benefit in patients treated within 2 hours of onset of STEMI than in those treated later.14

**Limitations of Thrombolysis**

1. **Contraindications**

Despite the benefits of thrombolytic therapy and its ease of administration, there are a number of contraindications forbidding its use.15 TIMI 9 registry has shown that 10.3% of patients had contraindications for the use of thrombolytic therapy.15

The absolute contraindications are:

- Oral anticoagulant therapy
- Pregnancy or within 1 week postpartum
- Uncontrolled hypertension (BP > 180/110 mmHg)
- Advanced liver disease
- Infective endocarditis
- Peptic ulcer
- Refractory resuscitation

2. **Elderly population**

There is an increase in mortality rate as the age increases.17 More evidence and clearer guidelines are required for thrombolytic therapy in patients of STEMI who are 85 years or older.

A scientific statement from the American Heart Association council for clinical cardiology18 summarized the thrombolytic treatment for the elderly STEMI population as follows:

i. Thrombolytic therapy as compared to no reperfusion therapy offers mortality benefit (that includes treatment-related deaths due to intra-cranial haemorrhage, stroke, shock and myocardial rupture) in the elderly population up to the age of 85 years

ii. Nonfatal strokes are rare (less than 3%) even amongst the subjects 85 years or older

iii. Reduced dosing of unfractionated heparin or adjusted doses of low molecular weight heparin minimize the risks of bleeding

iv. The risk of thrombolytic therapy in subjects 85 years or older remains high and more data is needed for clear guidelines

3. **Time Sensitivity**

Time sensitivity of thrombolytic therapy is well established. The earlier the treatment is instituted the greater is the benefit. In a meta-analysis of 22 trials comprising of 50,246 patients, the relationship between time delay in thrombolytic therapy and short term outcome in the form of 35 - day mortality was analysed. The results of thrombolytic therapy were substantially superior in patients presenting within 2 hours of onset of symptoms as compared to those presenting later.14 Thrombolytic therapy is more “time sensitive” as compared to primary PCI.

4. **Bleeding**

Hemorrhage is another important issue with thrombolytic therapy. Intracranial bleed is seen in 0.9 to 1.0 % of the total population studied.50 Major non-cerebral bleed occurs in 4 to 13% of patients treated with thrombolytics.10,19 The significant predictors of intracranial haemorrhage are old age, lower body weight, female gender, prior cerebrovascular disease and hypertension on admission.20

5. **Infarct Related Artery Patenty**

The issue of “Illusion of reperfusion” has often been raised (Figure 1). The 90 - minute patency rates vary from 50% with streptokinase to 75% with newer thrombolytics, whereas TIMI grade 3 flow correspondingly is seen in only 32% to 63% of treated. It is also clear that a patent epicardial coronary artery does not always mean effective tissue perfusion. Even with a patent coronary artery, there may be a decline in the benefit due to insufficient recanalization, TIMI grade 2 flow, residual stenosis, poor tissue perfusion, subsequent re-occlusion and reperfusion injury.21
6. Re-infarction and Recurrent Ischemia

Following thrombolytic therapy, there is a pro-coagulant period. Re-occlusion rate of the infarct related artery may be as high as 10% in hospital, and up to 30% by 3 months. Re-infarction rates have been reported to be around 5% in hospital and 7% within the first year of thrombolysis. Advances in adjunctive antiplatelet and anticoagulant therapies and close follow up have been able to overcome many of these problems.

Adjunctive anti-thrombotic therapy is indicated to increase the efficacy of thrombolysis and also minimise the risk of re-occlusion. The benefit of Aspirin in the management of STEMI is long established and is unequivocal. The Clarity – TIMI 28 as well as the COMMIT trials demonstrated the benefit of adding clopidogrel to aspirin and thrombolytic therapy. Heparin has long been used in the treatment of STEMI in association with thrombolysis, and has been shown to improve coronary patency following thrombolysis with tPA. The low molecular weight heparrin, enoxaparin, has substantial evidence in its favour for its use in the treatment of STEMI. Newer agents like Fondaparinux have also improved patient outcomes by preventing deaths and re-infarction, especially in those that receive Streptokinase. These adjunctive therapies have further enhanced the benefits of thrombolytic therapy.

Thrombolysis vs Primary PCI

Over the last several years, the field of Interventional Cardiology has demonstrated the superiority of primary PCI over thrombolytic therapy in the management of acute STEMI.

Benefits

Coronary flow restoration is achieved in a higher number of patients with primary PCI as compared to thrombolytic therapy. Widimsky et al and Anderson et al have shown that while primary PCI restores coronary flow in 90% of patients of acute STEMI, it is seen in only 40-60% of patients treated with thrombolytic therapy. A quantitative review of 23 randomised trials clearly demonstrated a significant mortality benefit with primary PCI (5%) when compared with thrombolytic therapy (7%).

Limitations

Lack of primary PCI facility and capability in majority of centres globally in general and in India in particular is a major drawback. It is also a more expensive therapeutic strategy, which many in our country can ill afford. Due to infrastructural constraints, many centres may not have PCI facility available round the clock, and some centres may not be achieving the ideal door to balloon time or first medical contact to balloon time. Another major impediment would be the distance to travel from non-PCI capable centre to PCI-capable centre. Streamlined STEMI care and medical networking in the health care system are yet to catch the imagination our health care authorities, especially in our country.

Data from CREATE registry from India gives an insight into the role of reperfusion therapies in STEMI in India. In a study population of 20,468 patients who had a definitive diagnosis of acute coronary syndrome, the median time from symptom onset to hospitalisation was 360 minutes; of patients who had STEMI, 58.5% received thrombolytic therapy and 15.3% received primary PCI. 72.1% of patients came from lower middle class and poor class.

Current Scope of Thrombolysis

Considering the relative advantages and disadvantages of thrombolysis and Primary PCI, one has to individualize the choice of therapy of each patient. The following need to be borne in mind while considering the option of thrombolytic therapy in any patient.

1. Thrombolytic therapy is beneficial, easily accessible and affordable. Even in the elderly, thrombolysis is clearly better than no treatment.
2. Thrombolytic agents can be administered as a bolus.
3. When transfer delay is a problem, thrombolysis is a good option. In such situations, how quickly the reperfusion therapy is delivered is more important than which reperfusion therapy is offered.
4. Primary PCI has constraints in terms of cost, availability, accessibility and expertise while at the same time delivering better patient outcomes.

What do the Guidelines Say?

Guidelines for managing patients with STEMI are available from various professional bodies, notably from the American College of Cardiology / American Heart Association (ACC / AHA), the European Society of Cardiology (ESC), and the Association of Physicians of India (API).

Guidelines from Association of Physicians of India lay down the indications for thrombolytic therapy in STEMI as follows:

1. Early presentation (3 hours or less from symptom onset and there is a delay in invasive therapy)
2. Invasive strategy is not an option:
   - Catheterization laboratory not available / occupied.
   - Financial reasons
   - Lack of access to a skilled PCI laboratory
   - Vascular access difficulties
3. Delay to invasive strategy
   - Prolonged transport: (door to balloon) – (door to needle) time is greater than one hour
   - Medical contact to balloon or door to balloon time is greater than 90 minutes

ACC/AHA Guidelines (2007 STEMI Focused update recommendations) are as below:

Class I Recommendations are:

1. STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within 90 minutes of

![Fig. 1](image-url) : Infarct related artery patency

<table>
<thead>
<tr>
<th>Time</th>
<th>Patency</th>
<th>Reocclusion</th>
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<tr>
<td>60-min</td>
<td>75%</td>
<td>44%</td>
</tr>
<tr>
<td>90-min</td>
<td>85%</td>
<td>29%</td>
</tr>
<tr>
<td>TIMI 3 flow</td>
<td>57%</td>
<td>25%</td>
</tr>
<tr>
<td>No myocardial perfusion</td>
<td>23%</td>
<td>25%</td>
</tr>
<tr>
<td>Intermittent patency</td>
<td>34%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Fig. 1: Infarct related artery patency
first medical contact as a systems goal. (Level of Evidence: A)

2. STEMI patients presenting to a hospital without PCI capability and who cannot be transferred to a PCI center and undergo PCI within 90 minutes of first medical contact should be treated with thrombolytic therapy within 30 minutes of hospital presentation as a systems goal unless thrombolytic therapy is contraindicated. (Level of Evidence: B)

ESC Guidelines state the following for thrombolytic therapy in patients with STEMI:

Thrombolytic therapy should be used in the absence of contraindications and if primary PCI cannot be performed within the recommended time (I A)

A fibrin-specific agent should be given (I B)

Pre-hospital initiation of thrombolytic therapy (IIa A)

These guidelines clearly state that “The emphasis on primary PCI should not obscure the importance of thrombolytic therapy.” The critical factor in reducing morbidity and mortality is the time to treatment from onset of symptoms of STEMI.

Many centres treating STEMI in our country and also globally do not have PCI capability and many interventional cardiology centres do not meet the time goal for primary PCI. Thrombolytic therapy is preferred under these circumstances.

Innovations in Thrombolytic Therapy

There are two well-defined areas where thrombolytic therapy may continue to have a prominent place.

A. Pre - hospital Thrombolysis
B. Pharmaco-invasive therapy.

Pre - hospital Thrombolysis:14,35,36

Since “time is muscle and muscle is life”, it is logical to raise the issue of the role of pre-hospital thrombolysis. Several registries, post-hoc analyses, randomized control trials and meta-analysis have shown that pre-hospital thrombolysis is feasible and clinically useful in improving the outcome of patients with STEMI. One study involving more than 6000 patients showed that pre-hospital thrombolysis as compared to in-hospital thrombolysis was associated with a significant 17% reduction in early mortality.35 A meta-analysis of 22 trials highlighted the larger mortality reduction in patients treated within 2 hours of onset of symptoms than in those treated later.34

A 5 - year follow up of CAPTIM trial36 concluded that mortality is similar for primary PCI as compared to the use of a policy of pre - hospital thrombolysis followed by transfer to a PCI capable centre. It also showed that patients treated within 2 hours of symptoms had a lower 5 - year mortality with pre-hospital thrombolysis.

Pharmaco-Invasive Therapy (Figure 2)

We also need to overcome another limitation of the thrombolytic therapy, and that is “reocclusion” of the infarct related artery leading to re-infarction and poor outcome. The reocclusion rate following thrombolysis is 10% in-hospital and 30% during the first year.26 Apart from the adjunctive therapy with anti-platelets and anti-thrombetics, a routine PCI after 3 hours and before 24 hours is an attractive option.27 In CARESS trial,27 a more conservative strategy (i.e. angiogram only in cases of failed thrombolysis) was associated with a worse clinical outcome than the strategy of angiogram and intervention (if indicated) in all cases following thrombolysis (the pharmaco - invasive strategy).

TRANSFER AMI study38 showed that patients coming to non-PCI centres when transferred for PCI within 6 hours of thrombolysis had fewer ischemic complications than those patients receiving standard treatment (i.e. rescue PCI or delayed angiography). A meta-analysis demonstrated significant mortality benefit at 30 days and one year with early transfer of patients for PCI subsequent to thrombolysis as compared to ischemia guided intervention.39

NORDISTEMI trial40 also showed a significant reduction in the composite of death, re-infarction, stroke or recurrent ischemia at one year in the group of patients undergoing immediate transfer and PCI following thrombolysis as compared to those in the conservative treatment arm.

Conclusion

Thrombolytic therapy will continue to have a major role in the management of STEMI patients for many years to come. Where Primary PCI facilities are not available or time delay to PCI is expected to be too long, thrombolytic therapy should be offered promptly. After thrombolysis, whether pre - or in - hospital, the patient should be transferred to a PCI facility immediately. A system for STEMI care with networking of centres and streamlining of procedures should evolve to enable optimal management of patients with STEMI.

References


