Present Status of Pre-hospital Thrombolytic Therapy for Acute Myocardial Infarction—Its Indications and Problems—

JMAJ 45(4): 143–148, 2002

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Abstract: Early administration of thrombolytic drugs for acute myocardial infarction may improve survival if safely and appropriately administered. Delays to thrombolytic reperfusion are substantial and are key factors in efforts to improve thrombolytic strategies. Transportation delays vary depending on the patient’s distance from the hospital and availability of local ambulance system. In-hospital delay is also a large single component of delay. Intuitively, pre-hospital initiation of thrombolytic therapy is the most promising approach to reducing the overall time to therapy. A meta-analysis of 6 randomized controlled trials of pre-hospital versus in-hospital thrombolysis for acute myocardial infarction indicated significantly decreased all-cause hospital mortality among patients treated with pre-hospital thrombolysis compared with in-hospital thrombolysis. Estimated time to thrombolysis was 104 minutes for the pre-hospital group and 162 minutes for the in-hospital thrombolysis group. However, the time savings can be offset in most cases by an improved hospital triage with resultant “door-to-needle time” reduced to 30 minutes or less. Furthermore only a small percentage (5% to 10%) of patients with chest pain in the pre-hospital setting have acute myocardial infarction and are eligible for thrombolytic therapy. For these reasons, a general policy of pre-hospital thrombolytic therapy cannot currently be advocated and indicated only in cases with transport time greater than 60 or 90 minutes as a Class IIb recommendation in the ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction.

Key words: Acute myocardial infarction; Coronary thrombolysis; Pre-hospital thrombolysis; t-PA

Introduction

Approximately one half of the patients died of acute myocardial infarction (MI) die within 1 hour of onset of symptoms and before reaching a hospital. Coronary reperfusion therapy in...
evolving acute MI is an established and effective therapy for reduction of mortality and morbidity. More recent data regarding the time-dependent benefits of reperfusion therapy provide added stimulus to develop more effective means of expediting delivery of medical care to patients with acute MI. The reperfusion therapy is not limited just to the widespread use of thrombolytic agents, but also PTCA, stent and even emergency CABG surgery in suitable patients. Currently PTCA and stent implantation therapy is more frequently performed than thrombolysis in Japan.

Delay in treating patients with acute MI is a critical factor in decreasing the overall survival rate. Boersma et al.\(^2\) reported that the relation between treatment delay and mortality reduction was expressed better by a non-linear than linear regression (Fig. 1), and the beneficial effect of fibrinolytic therapy is substantially higher in patients presenting within 2 hours after symptom onset compared to those presenting later. The components of delay from onset to treatment are (1) patients related (i.e., failure to recognize the seriousness of the symptoms and delay in seeking medical attention); (2) pre-hospital evaluation, treatment, and transport times; and (3) time required for diagnosis and initiation of treatment in the hospital. In most cases, patient-related delay is the longest. Interventions to minimize patient delay are primarily educational in nature. As for the reperfusion therapy, pre-hospital initiation of thrombolytic therapy may be the most promising approach to reducing the overall time to therapy.

In this article, randomized controlled trials of pre-hospital versus in-hospital thrombolysis for acute MI were reviewed and its indications and problems were discussed.

**Indications and Contraindications of Thrombolysis**

1. **Indications of Thrombolysis**

Recent ACC/AHA guidelines\(^3\) are as follows; Class I (conditions for which there is evidence and/or general agreement that given procedure or treatment is beneficial, useful, and effective) are 1) ST elevation, time to therapy 12 hours or less, age less than 75 years, and 2) bundle branch block and history suggesting acute MI. The earlier therapy begins, the better the outcome, with the greatest benefit decidedly occurring when therapy is given within the first 3 hours; proven benefit occurs, however, up to at least within 12 hours of the onset of symptoms.

Class IIa (conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. And weight of evidence/opinion is in favor of usefulness/efficacy) is 1) ST elevation, age 75 years or older. In persons older than 75 years, the overall risk of mortality form MI is high without and with therapy. Although the proportionate reduction in mortality is less than in patients younger than 75, the absolute reduction results in 10 lives saved per 1,000 patients treated in those over 75.

Class IIb (usefulness/efficacy is less well established by evidence/opinion) are 1) ST elevation, time to therapy greater than 12 to 24 hours, and 2) blood pressure on presentation greater than 189 mmHg systole and/or greater than 110 mmHg diastole associated with high-risk MI.

Class III (conditions for which there is evidence and/or general agreement that a proce-
PRE-HOSPITAL THROMBOLYTIC THERAPY

2. Contraindications and Cautions for Thrombolysis

Bleeding represents the most important risk of thrombolytic treatment. Contraindications and cautions for coronary thrombolysis are shown in Table 1.3)

<table>
<thead>
<tr>
<th>Contraindications</th>
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<tr>
<td>Previous hemorrhagic stroke at any time; other strokes or cerebrovascular events within 1 year</td>
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<tr>
<td>Known intracranial neoplasm</td>
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<tr>
<td>Active internal bleeding (does not include menses)</td>
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<td>Suspected aortic dissection</td>
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<tr>
<th>Cautions/relative contraindications</th>
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<tr>
<td>Severe uncontrolled hypertension on presentation (blood pressure &gt;180/110 mmHg)</td>
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<tr>
<td>History of prior cerebrovascular accident or known intracerebral pathology not covered in contraindications</td>
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<td>Current use of anticoagulants in therapeutic doses (INR ≥2–3); known bleeding diathesis</td>
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<tr>
<td>Recent trauma (within 2–4 weeks), including head trauma or traumatic or prolonged (&gt;10 min) CPR or major surgery (&lt;3 wk)</td>
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<tr>
<td>Noncompressible vascular punctures</td>
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<tr>
<td>Recent (within 2–4 weeks) internal bleeding</td>
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<tr>
<td>For streptokinase/anistreplase: prior exposure (especially within 5 d–2 y) or prior allergic reaction</td>
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<tr>
<td>Pregnancy</td>
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<tr>
<td>Active peptic ulcer</td>
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<td>History of chronic severe hypertension</td>
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Table 1 Contraindications and Cautions for Thrombolytic Use in Myocardial Infarction

Thrombolytic Agents and Routes of Administration

All of the thrombolytic agents currently available are plasminogen activators. However, aside from this similarity, there are many differences among agents in dose, circulating half-life, fibrin-specificity, rates of coronary recanalization, risks of hemorrhage, and cost. Thrombolytic agents available in Japan are urokinase, tissue plasminogen activator (alteplase, tisokinase, nateplase), pro-urokinase (nasaruplase), and mutant or modified plasminogen activator (monteplase, pamiteplase). Among them urokinase, tisokinase, and nasaruplase are approved for intracoronary use as well as intravenous use, but this intracoronary route of administration for acute MI has been now less frequently performed. Modified plasminogen activators have a longer half-life and can be administered with a single bolus intravenous injection.

Recent trials with alteplase have used an accelerated or frontloaded dosing regimen.4) Because the accelerated regimen leads to greater early patency rates without an increase in hemorrhagic risk, it has become the preferred method of administration in the United States and Europe. Modified t-PA monteplase has also proved to produce a higher rate of early recanalization of the infarct-related coronary artery without fatal bleeding complications.5)
Pre-hospital Thrombolysis

In the randomized Seattle Myocardial Infarction Triage and Intervention (MITI) study, cardiac function and infarct size were assessed in rather small number of patients who received either in-field or in-hospital treatment with t-PA. Though the time savings for the pre-hospital thrombolysis conducted by paramedics per se was small (about 30 minutes), treatment initiated in less than 70 minutes of onset of symptoms was found to result in a distinct advantage in left ventricular function, infarct size, and mortality. The larger European Myocardial Infarction Project (EMIP) study randomized 5,454 patients to pre-hospital versus in-hospital treatment with APSAC (anisoylated plasminogen streptokinase activator complex) and assessed mortality outcome. Patients were treated somet warm later in-field in EMIP (at about 2 hours) than in MITI (about 1 hour), but about 1 hour was saved by in-field treatment compared with in-hospital therapy. This study showed a significant reduction of cardiac mortality and non-significant total mortality at 1 month.

Morrison et al. reviewed randomized controlled trials of pre-hospital versus in-hospital thrombolysis for acute MI and performed meta-analysis measuring in-hospital mortality in 6 randomized trials including MITI and EMIP (n = 6,434). Results were similar regardless of trial quality or training and experience of the provider among the trials and all-cause mortality was significantly decreased in pre-hospital thrombolysis group as compared with in-hospital group (Fig. 2). Estimated time to thrombolysis was 104 minutes for the pre-hospital group and 162 minutes for the in-hospital group. However, the time savings can be offset in most cases by an improved hospital triage with resultant “door-to-needle time” reduced to 30 minutes or less. Furthermore, only a small percentage (5% to 10%) of patients with chest pain in the pre-hospital setting have acute myocardial infarction and are eligible for thrombolytic therapy. For these reasons, a general policy of pre-hospital thrombolytic therapy cannot currently be advocated and indicated only in cases with transport time greater than 90 minutes as a Class IIb recommendation in the ACC/AHA Guidelines for the Management of Patients with Acute Myocardial Infarction.

Choice of Agent

Three mega-trials randomizing a total 103,069 patients have compared the effects on mortality of various thrombolytic agents. In the Interna-
tional Study including GISSI-2 20,891 patients were randomized to receive either streptokinase or alteplase.9) Mortalities at 30 days were similar (8.9% with streptokinase versus 8.5% with alteplase). The ISIS-3 trial randomized 41,299 patients to receive either streptokinase, anistreplase, or duteplase.10) Mortality was similar with all three thrombolytic regimen: 10.5% with streptokinase, 10.3% with duteplase, and 10.6% with anistreplase. The GUSTO-I trial randomized 41,021 patients to receive one of four thrombolytic regimens.11) The lowest mortality rate at 30 days (6.3%) was achieved with accelerated administration of alteplase as compared with 7.2% for streptokinase. Why did ISIS-3 and International Study fail to demonstrate any mortality difference between streptokinase and t-PA, as GUSTO-I trial did? The failure to use intravenous heparin in the former trials may have disadvantaged alteplase in International Study and duteplase in ISIS-3. Secondly a standard 3-hour infusion of alteplase has been shown to produce less 90-minute patency than an accelerated alteplase regimen, which delivers substantially more of the drug to average-weight patients in the first 60 minutes.

Recently the ASSENT-2 trial assessed the efficacy and safety of modified t-PA tenecteplase compared with alteplase.12) Tenecteplase and front-loaded alteplase were equivalent for mortality. And the ease of administration of tenecteplase may facilitate more rapid treatment in and out of hospital. Similarly the InTIME-II trial demonstrated that 30 day mortality was equivalent but long-term mortality tended to be lower in the nPA (lanoteplase) group as compared with accelerated alteplase.13) Both of these agents have the advantage over alteplase of bolus intravenous administration, and therefore could easily be given in the community or pre-hospital phase.

New Adjunctive Therapy

The disadvantage of thrombolytic therapy over primary angioplasty has been said to be a relatively low TIMI-3 flow of approximately 50%. In the TIMI-14 study, however, TIMI-3 flow was obtained in 77% at 90 minutes after start of the fibrinolytic regimen.14) The TIMI-14 regimen consisted of half the standard dose of alteplase, a low dose of intravenous heparin, monoclonal antibody of platelet glycoprotein IIb/IIIa receptor, abciximab, and aspirin. At 60 minutes 65% of patients had TIMI-3 flow. These findings are significant since only 54% of patients given alteplase in the GUSTO-I angiographic substudy15) had TIMI-3 flow at 90 minutes, and since coronary angioplasty commonly takes longer than an hour and a half of complete.

REFERENCES

7) The European Myocardial Infarction Project


