Review Article

What is the likely benefit of earlier thrombolysis?

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Introduction

Theory, experiment, and common sense all suggest that the earlier thrombolysis is given for acute myocardial infarction, the greater should be the benefit. We would expect the time-effect, i.e. the increased efficacy of thrombolytic therapy with earlier administration, to be very powerful, and of immense clinical importance. However, from randomized clinical trials it appears that the benefit of earlier thrombolysis is only very modest. The results of clinical trials, therefore, apparently conflict with our expectations based on theory and experiment. How can this be explained?

Patency rate and time of thrombolysis

Myocardial infarction is usually the result of occlusion of a coronary artery by thrombus forming on the newly exposed surface of a ruptured atheromatous plaque. New thrombus is less consolidated and extensive than it will later become, so the earlier that thrombolysis is attempted, the more successful it is likely to be.

In an angiographic study of 424 patients with acute myocardial infarction, the percentage with a patent infarct-related artery fell by 9% per hour of delay from onset of symptoms to administration of thrombolytic therapy\textsuperscript{111}. A negative correlation between times of thrombolysis and patency rates has also been reported in a comparison of various studies; the patency rate was typically 80% at 2 h and 50% at 4 h from onset\textsuperscript{111}.

Myocardial salvage and time of reperfusion

Following experimental coronary occlusion, myocardial infarction is not an immediate but a gradual process radiating out from the subendocardium to the epicardium. If reperfusion is established early enough there is no permanent damage; myocardial salvage is complete. Myocardial salvage is negligible when reperfusion is established after 4 h occlusion. For intermediate times the amount of salvage rises steeply with earlier reperfusion, particularly for times under 2 h\textsuperscript{112-116}.

In humans the time course of myocardial infarction and myocardial salvage appears to be similar to that in experimental animals, although the process may be modified by the extent of collateral flow to the region. An early study showed that infarction could be aborted by intracoronary streptokinase administered 1–2 h after symptom onset\textsuperscript{117}.

Mathey et al\textsuperscript{118} showed that wall motion abnormalities at follow-up were significantly less frequent in patients receiving thrombolysis within 2 h compared with later. The severity of hypokinesia correlated with peak serum creatine kinase, indicating that thrombolytic therapy initiated within 2 h reduces infarct size and improves regional left ventricular function more than therapy given later.

The European Cooperative Study Group reported that infarct size was lower with earlier thrombolysis, the relationship being non-linear, with a marked reduction in infarct size when treatment was commenced within 75 min of onset\textsuperscript{119}.

In the myocardial infarction triage and intervention trial (MITI), infarct size was less, left ventricular function was increased, and 1-month mortality was reduced in patients receiving t-PA within 70 min of onset compared with later administration\textsuperscript{120}. The infarct was too small to be visualized by tomographic thallium scan in 40% of patients receiving therapy within 3 h of onset.

On the other hand, in a trial in Western Washington, infarct size was not demonstrably reduced by thrombolysis given more than 3 h from onset\textsuperscript{121}. In a trial of intravenous streptokinase in acute myocardial infarction (ISAM), left ventricular ejection fraction in patients with anterior infarction was higher in those receiving streptokinase rather than placebo, but only when it was given within 3 h of onset; patients treated after 3 h did not differ from their respective controls\textsuperscript{122}.

Key Words: Acute myocardial infarction, thrombolytic therapy, time delay.
Evidence of the time-effect from clinical trials

In the first large randomized trial of thrombolysis to show mortality benefit (GISSI), the relative risks were 0.74, 0.80, 0.87 and 1.19 for 0–3, 3–6, 6–9 and 9–12 h subgroups\textsuperscript{[13]}\textsuperscript{[13]}\textsuperscript{[13]}\textsuperscript{[13]}. In patients randomized within an hour of onset, the relative risk was 0.49. This result seemed to fulfill the expectation that thrombolysis should be more effective earlier than later. However, the FTT overview of all randomized trials over 1000 patients confirmed that there was significant benefit from thrombolysis 6–12 h from onset\textsuperscript{[17]}\textsuperscript{[17]}\textsuperscript{[17]}\textsuperscript{[17]}. The average time of randomization for patients with ST elevation or bundle branch block block included in the overview was 6.7 h. Thus, most trial patients received thrombolytic therapy too late for myocardial salvage to have been the mechanism of benefit. It is now generally accepted that restoring the patency of the infarct-related artery several hours after occlusion is beneficial, not by myocardial salvage, but by increasing the electrical stability of the infarct, and by preventing remodelling, infarct expansion, and heart failure\textsuperscript{[18]}\textsuperscript{[18]}\textsuperscript{[18]}\textsuperscript{[18]}. These processes seem to be largely independent of the time after occlusion when reperfusion is established.

FTT estimate of loss of benefit by thrombolysis delay

The FTT overview reports that over the period 0–24 h after onset of symptoms, the absolute benefit of thrombolysis compared with control increases linearly with earlier randomization\textsuperscript{[17]}\textsuperscript{[17]}. Extrapolated to zero hours the difference is 3.5% or 35/1000, while at 21:5 h it is zero. The loss of benefit per hour of delay to randomization is 1.6 per 1000 patients treated. However, while reliably indicating the average loss of benefit by delay, this analysis seriously underestimates the benefit of earlier thrombolysis. The mechanism of benefit for the bulk of patients in the overview was not myocardial salvage, yet these patients would have carried most weight in the prediction of mortality at a time when myocardial salvage is probable. The use of the FTT data to predict what might happen within the first hour of infarction is particularly unsafe because relatively few patients presented at that time, and none at time zero. On the other hand many patients included in the overview presented 13–24 h after symptom onset, so the prediction of the time after onset when thrombolysis is no longer effective is reliable, no extrapolation being needed.

But there is another reason why the benefit of earlier thrombolysis is underestimated by the FTT analysis. In Fig. 1 are plotted the mortality rates for patients with ST elevation or bundle branch block block randomized to thrombolytic therapy or control at 0–1, 2–3, and 4–6 h from onset. Data from Fig. 3 of FTT overview\textsuperscript{[16]}\textsuperscript{[16]}\textsuperscript{[16]}\textsuperscript{[16]}.
Design of a trial to quantify the time-effect

Because of the way patients behave in the early hours after onset of symptoms — those with more severe myocardial infarction tending to call for medical help sooner[19,20] and older patients tending to call late[21-23] — time of presentation is confounded with severity of infarction. If the outcome for patients given thrombolytic therapy as soon as they present is considered in relation to the time of treatment, the benefit of earlier thrombolysis is underestimated because it is the sickest patients who receive the earliest treatment. In order to quantify the time-related benefit of thrombolysis, time of presentation has to be dissociated from time of treatment: patients must be randomly allotted thrombolysis on presentation, or after a deliberate delay. Ideally, the delay should be substantial, and the timing of early or late thrombolysis should be the same for all patients, say 2 and 4 h after onset. But it is generally accepted that earlier treatment is better than later treatment; only the magnitude of this time-effect is unknown. It is therefore considered unethical to delay thrombolysis beyond the time when it might ordinarily be given. Hence the design of a trial to quantify the time effect is constrained by ethical and practical considerations[24]. The trial cannot be conducted entirely in hospital because the late group would receive less than the best available treatment. The late group should be treated as soon as possible after arriving in hospital, and the early group as soon as possible after they have presented in the community. The late group then receive standard care, and the early group has better than standard care, and the ethical objections are met. However, modification of the ideal trial design so that early and late treatments are given as soon as practicable weakens the trial’s ability to answer the question posed: what is the magnitude of the benefit from earlier thrombolytic therapy? This is because the times of treatment in the early and late groups overlap with each other, effectively reducing the number of patients in the trial. An analogy may be drawn with a dose comparison trial; such a trial would be vitiated if the doses actually received varied substantially, especially if those of one group overlapped with those of the other. But in trials of prehospital thrombolysis, there is considerable overlap between the times of prehospital thrombolysis, in none did

**Figure 2** Possible relationship between mortality rate and time of thrombolysis for patients presenting in hospital 2-3 h (mean 2-5 h) after onset. See text.

**Limits of the benefit gradient**

The FTT estimate of the time-related benefit of thrombolysis is misleading, especially for predicting the result of earlier treatment. The benefit of earlier treatment is much greater than the FTT estimate, whereas the loss of benefit for later treatment is close to the FTT estimate.

The two points plotted in Fig. 2 represent the mortality rates for patients randomized to thrombolytic therapy or control (8.4 vs 11.4%) at an average time of 2-5 h from onset of infarction; they are taken from Fig. 1. Let us suppose that reperfusion had been established immediately at onset in the treatment group, and that none had died. The average benefit gradient over the period 0-2-5 h would then have been 8.4%/2.5 = 34/1000 h^-1 (dashed line). This marks the greatest possible average benefit from earlier thrombolysis. But the gradient would probably be steeper in the earlier than the later part of the period, so the gradient in the region of 2-5 h would therefore be less than 34/1000 h^-1. Had these patients been treated in hospital after such a long delay that the treatment had completely lost its efficacy, at 21-5 h from onset, the mortality rate would then have been the same as in the control group. The average benefit gradient over the period 2-5-21 5 h would then be (11.4%-8.4%)/(21.5-2.5)=1.6/1000 h^-1. Again, it is likely that the gradient would be steeper in the earlier part of this time period than at the end, and the relationship between mortality rate and time of thrombolysis over the period 0-6 h would be something like that shown by the continuous curved line.

By the same reasoning the limiting benefit gradients for patients presenting up to 1 h from onset (mean 0.98 h) would be 94/1000 h^-1 and 1.9/1000 h^-1 for treatment before or after hospital presentation respectively. The FTT data are thus compatible with a very wide range of benefit gradients for thrombolysis given at an earlier time than was actually the case.

**Trials of prehospital thrombolysis**

The three largest randomized trials comparing prehospital with hospital thrombolysis are EM1P[25], MITI[110], and GREAT[26], with 5469, 360, and 311 patients, respectively. It should be noted that EM1P terminated prematurely because of lack of funds, and neither MITI nor GREAT were designed as mortality endpoint trials. Although in all three trials the mortality was lower with prehospital than with hospital thrombolysis, in none did...
The survival curves for the two published recently undertaken and the results up to 30 months have been overview, being less than the limiting gradient, and of confidence intervals to this benefit gradient would be to give a spurious impression of reliability, but this, though tentative, is the best estimate we have of the time-related benefit. Soon after the onset of symptoms there is less ischaemic time is short, all three factors making for greater the benefit. The earlier thrombolysis is started, the greater the benefit. Soon after the onset of symptoms there is less coronary thrombus, the thrombus is easier to lyse, and ischaemic time is short, all three factors making for myocardial salvage and smaller infarcts. There is a wealth of clinical evidence to show that thrombolysis initiated within 2 h of onset is much more effective than if it is started later. But in spite of all these expectations, there is scant evidence from clinical trials that mortality from acute myocardial infarction is reduced by very much more if the treatment is given earlier: the most authoritative estimate from the FTT collaborative group puts the additional benefit at only 1-6/1000 h⁻¹. However, this overview was heavily weighted by patients treated too late for myocardial salvage to have been the mechanism of benefit, and it does not preclude the possibility that the additional benefit from earlier thrombolysis is very much greater than the loss of benefit from later thrombolysis.

The benefit of earlier thrombolysis can only be quantified by a trial design in which patients are randomly allotted thrombolysis on presentation or after a deliberate delay. Such trials are few in number and small in size, and because of ethical and practical consideration, the ideal design is compromised, with loss of power as a result. Inspection of the results of the three largest such trials suggests that the time-related benefit is of the order of 20/1000 h⁻¹ within 1 month. If thrombolysis is given early enough for myocardial salvage to occur, groups diverge, so that the differences in mortality between prehospital and hospital groups are 5, 11, and 15% at 30 days, 1 year, and 3 months, respectively. Statistical significance was achieved by 3 months, and at 30 months, P=0.0014 (difference 15%, 95% confidence interval, range 6-25%). This mortality difference resulted from a time-saving of 139 min, so the crude benefit gradient at 30 months is 66/1000 h⁻¹ (95% CI, range 25-106). The lower confidence interval of the benefit gradient at 30 months exceeds the 30 day estimate of 23/1000 h⁻¹ from all three trials. These decisive results at 30 months add to the credibility of the results at 30 days.

Reverting to the analogy with a dose comparison trial, one solution to the problem of overlapping doses in the high and low dose groups would be to construct a dose-response curve. In this way every patient would contribute to the result whatever the dose received. Multivariate logistic regression has been carried out on the 30-month results from GREAT in order to construct the temporal equivalent of a dose-response curve from which the benefit/time gradient may be calculated. By this analysis, for patients presenting prehospital 2 h after symptom onset, for every hour's delay in giving thrombolytic therapy there are 21/1000 (95% CI, range 1-94) additional deaths in 30 days and 69/1000 (95% CI, range 16-141) in 30 months.

Conclusions

In Fig. 3, the 1-month mortality rates for prehospital and hospital groups are plotted against median times of administration of thrombolytic agent. The benefit gradients range from 14/1000 h⁻¹ for EMIP, to 44/1000 h⁻¹ for MITI. The steepest gradient is in the trial with the earliest time of prehospital thrombolysis, and vice versa. Statistically speaking, there is no proper way of averaging these gradients, short of pooling the results of the three trials. But the line of best-fit between the six points has a gradient of 23/1000 h⁻¹. To give confidence intervals to this benefit gradient would be to give a spurious impression of reliability, but this, though tentative, is the best estimate we have of the time-related benefit of thrombolysis, being based on intention-to-treat analyses of the three largest appropriately designed trials. This gradient is quite consistent with the FTT overview, being less than the limiting gradient, and of the same order of magnitude as the gradient illustrated in Fig. 2.

Follow-up of GREAT

Long-term follow-up of the patients in GREAT is being undertaken and the results up to 30 months have been published recently. The survival curves for the two
i.e. within the first 2 h, there may be in addition very substantial deferred mortality benefits during the first few years of follow-up.

Thrombolysis has been described as the most important development in the treatment of acute myocardial infarction since the introduction of the defibrillator. But defibrillation is palliative, whereas thrombolysis, given early enough, corrects the underlying pathophysiology. In terms of its potential for saving life, early thrombolysis is as important as defibrillation, and just as urgent[10].

References