Editorial

THROMBOLYSIS IN MYOCARDIAL INFARCTION

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The pioneering work of Dewood et al in 1980 first demonstrated angiographically that there was a very high incidence of total coronary occlusion of the infarct-related artery in acute myocardial infarction (MI) [1] and subsequently it was shown that in most cases there was a thrombus associated with a ruptured or fissured plaque at the site [2]. These early studies provided the impetus for the reevaluation and reassessment of the role of thrombolytic agents in acute MI and the GISSI trial established the usefulness of intravenous streptokinase in this situation [3]. Thereafter there have been several megatrials which have looked into various aspects of thrombolytic therapy [4-8].

Of the various thrombolytic agents, streptokinase (SK) was the first to be available in the late 1950s and its use in acute MI was firmly established by the GISSI report [3]. It remains the most widely used agent with the major disadvantage being hypotension and allergic reactions. Tissue plasminogen activator (t-PA) was first used in 1981 [9] and with its being produced by recombinant techniques, rt-PA became widely used in the West. Its usefulness has been reemphasised recently by the GUSTO trial [8]; the major theoretical advantage of rt-PA is its clot-selectivity, short half life and the absence of allergic reactions while its cost remains its major limiting factor. Anisoylated plasminogen-streptokinase activator complex (APSAC) is another clotselective agent which has been tried - its advantage being the ability to give it rapidly as a bolus within a few minutes and the lack of allergic reactions. Urokinase and prourokinase have not been tried very extensively in the setting of acute MI.

Despite the number of agents available and the trials quoted in which these drugs were studied extensively, there are still many areas of controversy - as a result of which, even in a country like the USA, only a quarter to a third of all patients of acute MI actually receive thrombolytic therapy. These areas of controversy include the time window for administering the agent, its use in elderly patients, in patients with non-Q MI and unstable angina, in patients with non-diagnostic ECGs and the optimal adjunctive therapy.

The earliest trial which looked into the time-window question was the GISSI trial [3]. In this study, patients were enrolled upto 12 hours of onset of chest pain and benefit was shown to be a direct function of the time lapse from the onset of pain. The benefit for patients reporting beyond 6 hours was not found to be statistically significant. This report led to the recommendation for the use of thrombolytic agents only within the first 6 hours. The more recent GUSTO trial also only included patients who came within the first 6 hour time frame [8]. However, other studies such as the LATE trial [6] and the EMERAS report [7] considered patients reporting beyond this time frame. Thus, in the LATE trial using alteplase (rt-PA) there was significant reduction in mortality even in patients receiving the drug after 6 hours (8.9% vs 11.97% for placebo) but with a smaller reduction if given

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beyond 12 hours. The EMERAS study reported a definite but non-significant trend towards lower mortality with SK in patients given the drug between 7-12 hours and no improvement if given after that period. Based on these observations, it would be wise to recommend thrombolytic therapy to patients reporting within 12 hours of onset of chest pain.

Elderly patients were being denied thrombolysis in MI primarily because of the fear of strokes. However, with the population of the country getting older, the number of elderly patients with MI reporting to the CCU will keep on increasing. Hence, the relative contra-indication for thrombolysis in the elderly needs to be reviewed. The GISSI trial showed reduction in mortality in all age groups but this reduction did not reach statistical significance in those over 65 years while the incidence of strokes was low (0.2%)[3]. Other studies such as the ISIS - 3 [5] and the report by Maggioni et al [10] have shown that the incidence of strokes are more with t-PA rather than with SK. The FTT Colloborative Group, analysing data from various trials, also addressed this question and reported that after an initial higher mortality during the first day, elderly patients showed significant benefit from thrombolytic therapy between days 2 to 35 [11]. Even in the pre-thrombolytic era, strokes were a known complication and were usually embolic in nature and the incidence was 2-3%. This ceiling of 2-3% has not been exceeded in any of the trials with thrombolytic agents so far. Based on these, it would be prudent to recommend that elderly patients not be denied thrombolytic agents unless otherwise contraindicated and the only decision that need be taken should be the type of agent (SK vs t-PA).

The use of thrombolytic agents in unstable angina and non-Q infarcts was addressed in the TIMI-IIIB trial [12]. These workers reported an overall 42-day incidence of MI of 7.4% in the group receiving t-PA as opposed to 4.9% of placebo while in patients with unstable angina, the rate of death or MI was 9.1% against 5.0% for patients on placebo. Based on these figures, the authors concluded that the use of a thrombolytic agent is not beneficial and may be harmful in these subsets of patients.

About 10% of patients are excluded from thrombolytic therapy solely on the basis of their ECGs. Patients with recent onset chest pain suggestive of an MI and with a new onset of LBBB have a high in-hospital mortality of around 25%. Thrombolytic therapy has been found to be protective in this group even though the ECG precludes the diagnosis of the site of infarct [11,13].

Adjunctive therapy in thrombolysis has so far concentrated on antiplatelet and anticoagulant drugs - mainly aspirin and heparin - with a view to achieve more complete recanalisation as well as to reduce restenosis. However, these drugs have had a limited impact on these aspects [14] while they have been associated with a higher incidence of bleeding complications in the megatrials [5,9]. In view of this, more specific thrombin inhibitors such as hirudin, hirugen and hirulog are being investigated. Other drugs being tried include thromboxane synthetase inhibitors and monoclonal antibodies against GPIIb/IIIa receptor on platelets. Other approaches include betablockers and calcium channel antagonists, ACE inhibitors, and magnesium.

Thrombolysis has also been used in other situations. While its role in cardiogenic shock is controversial [15] there are now definite indications for clot lysis as an adjunct to angioplasty particularly in recently occluded saphenous vein grafts and acute closure during angioplasty [16].

The ultimate basis for the use of thrombolytic agents to reperfuse the myocardium is the theory that an open artery will translate to improved survival. Enhanced survival rates with the use of these agents has been shown in all the megatrials; however, the mechanism of this improved survival is not as yet clear. Since poor left ventricular (LV) function is the strongest prognostic factor in MI [17] this was considered to be the

mechanism for salvage of patients after MI following thrombolysis. Various workers have shown that this is not necessarily so; patients receiving thrombolytic agents had improved survival over heparin or placebo even though they both had similar ejection fractions [18,19]. Despite the fact that myocardial salvage is unlikely after the first few hours, late reperfusion has also resulted in improved patient survival [6,7]. In view of these discrepancies, it is now felt that other mechanisms may play a role in this 'open artery' hypothesis such as prevention of ventricular remodelling, improving electrical stability of the myocardium and perfusion of "hibernating" myocardium [20].

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