



Editorial

What is the ideal fibrinolysis to PCI time: Pharmaco-invasive strategy with streptokinase?



1. Introduction

Benefits of primary percutaneous coronary interventions (PCI) over fibrinolysis are well known. As a matter of fact this is one of the few therapies in cardiology that account for mortality benefit.^{1,2} However, the availability of this therapy because of logistic and other constraints may be severely restricted. The national intervention council data from India shows that in the year 2011 around 21,000 primary PCI were undertaken. In a country with a population upwards of 1.3 billion and burden of ST elevation myocardial infarction (STEMI) estimated to be 30,00,000, this seems woefully inadequate (national primary PCI rate < 1%).^{3,4} Here, pharmaco-invasive therapy with fibrin specific thrombolytics is a reasonable alternative.^{5,6} However, in several countries it is not fibrin specific fibrinolytic that is widely available; rather it is still streptokinase (STK) which is not only continues to be widely available but also cheap, so much so that it continues to feature in the literature from less industrialized nations.^{4,7} However, a strategy using STK followed by primary PCI has not been well studied.

2. Facilitated PCI

Initially, combination of fibrinolytic and PCI were attempted with the premise that fibrinolytic therapy given in conjunction with PCI could improve the results of PCI. However, early studies performed nearly three decades ago were largely negative. O'Neill and co-workers in a small series of acute STEMI patients demonstrated that adjunctive IV STK therapy with PCI did not improve arterial patency, enhance early preservation of ventricular function or lower restenosis rates compared with plain PCI. Furthermore, with combined strategy (facilitated PCI); hospital course was longer, more expensive, and more complicated. However, the negative results at that time could be due to lack of stents or poor PCI hardware and delay in the duration from administration of fibrinolysis to actual performance of PCI.⁸ PRAGUE Trial performed a decade later, with an improvement in PCI hardware and shorter lysis-balloon time (<1 h after institution of STK infusion) still demonstrated disappointing results. Although facilitated PCI opened more than twice as many arteries than mere STK (47% vs. 27% TIMI-flow 2–3) still this did not result in better patient outcome than plain STK infusion. This could have been due to several factors: more bleeding complications (when two therapies were combined) but also curiously more thrombotic/

ischemic complications resulting in higher number of strokes and re-infarctions, probably because of pro-thrombotic effects of STK. Thus, this study confirmed the results of previous studies that even in the era of stents and sophisticated PCI hardware and despite a rapid lysis-balloon time, facilitated PCI may not be beneficial for every patient.⁹ Two other studies evaluated the use of more fibrin specific, non-STK fibrinolytic. The Assessment of Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction (ASSENT-4) trial randomized 1667 STEMI patients to facilitated PCI with tenecteplase versus primary PCI alone.¹⁰ Unfortunately, this trial required premature termination because the primary end-point – death or heart failure and other adverse events; like intracranial hemorrhages were elevated. Paradoxically in this study as well, ischemic events not attributable to bleeding risk were also increased. In this study increased ischemic risk was attributed to sub-optimal clopidogrel loading and very low use of glycoprotein inhibitors (~10%) in the facilitated arm. However, fibrinolysis on its own is known to activate platelets, requiring more than usual platelet inhibition. Another trial, the Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) trial evaluated 3 combinations of anti-platelet and fibrinolytic combinations: 1) reteplase (full dose or half dose) plus early administration of abciximab, plus PCI 2) early administration of abciximab plus PCI, and 3) only primary PCI.¹¹ They randomized 2452 STEMI patients which was 82% of the originally planned study size. While the primary end point, a composite of all-cause mortality, readmission for heart failure, ventricular fibrillation, or cardiogenic shock was similar in all the groups, TIMI non-intracranial major bleeding and minor bleeding were significantly higher for either abciximab or fibrinolytic facilitated PCI strategy as compared with mere primary PCI. Thus good platelet inhibition, achieved in this trial did not translate into any clinical benefit.

3. Pharmaco-invasive PCI

This led to the concept of pharmaco-invasive (PI) PCI. The philosophy of this approach is different from facilitated PCI; whereas facilitated PCI worked on assumption that addition of fibrinolytic could improve results of primary PCI, PI-PCI looked at the other end of spectrum i.e. in those patients where primary PCI could not be immediately offered - could a delayed PCI improve results of only fibrinolytic therapy. Thus the control arm in these trials was fibrinolytic therapy rather than primary PCI and it tested the strategy that fibrinolytic therapy given at non-PCI capable

hospital followed by transfer to a PCI capable hospital was better than only fibrinolysis. A small initial study, the Combined Abciximab Re-teplase Stent Study in Acute Myocardial Infarction (CARESS-AMI) randomly assigned 600 STEMI patients treated with a combination of half-dose reteplase and abciximab at a non-PCI capable center to either immediate transfer to the nearest PCI capable center or to management in a local hospital (with transfer only in case of clinically indicated rescue PCI).¹² In this study, the primary composite outcome (death, reinfarction, or refractory ischemia at 30 days), was found reduced in the immediate-PCI group. However, there was a non-significant increase in the rate of major bleeding in PCI arm. The most definitive evidence came from the Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) trial which randomized 1059 STEMI patients to receive tenecteplase at non-PCI centers followed by transfer to PCI capable hospital with a goal of performing coronary angiography and PCI of the infarct-related artery within 6 h after fibrinolysis or plain fibrinolysis with possibility of clinically indicated rescue PCI.¹³ Results revealed that while there was a significant reduction in the primary end point, a composite of death, re-infarction, recurrent ischemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days in the PCI-transfer arm, there was no significant differences in the rates of TIMI major or minor bleeding, transfusions or intracranial hemorrhages. While, the lower rate of bleeding in this study could be explained on the basis of advances in procedural care of PCI patient such as use of smaller sheaths, earlier sheath removal, more utilization of radial access, lower doses of anticoagulants used and the elimination of post-procedural infusions of heparin, the real difference between the PCI strategy in this study versus earlier strategy in facilitated PCI could be that PCI was performed at a median of 2.8 h after randomization (unlike immediate PCI in facilitated PCI studies) and only when persistent occlusion or substantial stenosis of the infarct-related artery was present. This optimal window after fibrinolysis (increased platelet activation that occurs immediately after the administration of tenecteplase may return back to near normal after around 3 h) may have allowed for better outcomes.

The study by Raja and co-workers in the current issue of Indian Heart Journal provides an indirect evidence of STK when used in P-PCI approach.¹⁴ Evaluating the impact of TN-STEMI programme where STK was used as a thrombolytic agent in nearly 95% cases, undergoing pharmaco-invasive strategy, they found improvement in infarct related artery patency rate, and reduction in thrombus burden translating into fewer readmissions and lower target revascularizations (even though overall MACE rates remained same). Admittedly, these benefits accrued as a result of reduction in ischemia, first medical contact times, but the fact that STK was the background therapy confirms its efficacy in this approach as well. Another intriguing aspect in this study is the mean lysis-to-angiogram time of 18.2 h. While every effort must be made to decrease the ischemia to reperfusion, first medical contact –to-ECG time, the time when angiography/angioplasty should be done after fibrinolysis remains controversial.^{15,16} Although fibrinolytic therapy by definition dissolves clots and thrombus, paradoxically, it can be pro-thrombotic as well. The mechanism behind this effect is generally two-fold: lysis of clots releases thrombin which has a pro-thrombotic effect, and the thrombolytic agents themselves may directly activate platelets. Any procedure done when pro-thrombotic effect is at its peak will have ischemic manifestations. Thus there seems to be an optimal time after administration of fibrinolysis when PCI is most likely to be beneficial. This timing may be the “best bet” based on the platelet aggregation inhibition and platelet activation characteristics of these agents. For fibrin specific agents like tenecteplase it may be more than 3 h (but within 24 h) after lysis. Streptokinase on the other hand may have

different platelet reactivity.¹⁷ In addition STK may induce thromboxane A2 synthesis and activate platelets by generating specific anti-STK antibodies.¹⁸ Thus a lysis to angiography time of around 18 h may not only be more convenient but may actually be more appropriate as well when STK is used as an agent. Future studies will be required to ascertain the optimal time after STK therapy when PCI is likely to be safest and most effective. Furthermore, there should be a move to incorporate STK into more meaningful, region specific guidelines.¹⁹

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