Strategies in mechanical interventions for acute MI: facilitated and rescue PCI

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ABSTRACT **Primary Percutaneous Coronary Intervention (PCI) is the superior strategy for treating acute ST-elevation myocardial infarction (STEMI) as an initial strategy within the first 6 hours from symptom onset. Facilitation of PCI by the use of pre-treatment, prior to planned PCI, with thrombolytic drugs or glycoprotein (GP) IIb/IIIa inhibitors has held theoretical promise for earlier infarct related arterial patency, but has failed to deliver on such promise.**

Thrombolysis as an initial strategy is inevitable in a large number of STEMI patients due to limited access to primary PCI. This strategy has limited success, and when it fails, rescue PCI has benefit and is recommended.

Mechanical methods such as thrombectomy and distal protection, while having an intuitively plausible mechanism for benefit, have also failed to meet expectations and have a limited role in acute STEMI. SAHeart 2008; 5:52-57

INTRODUCTION

Acute ST-elevation myocardial infarction (STEMI) is most often caused by thrombotic occlusion at the site of plaque rupture in a coronary artery.[1,2] The initial therapeutic goal is to achieve an open artery. Whatever method is used for reperfusion, this needs to be achieved in the shortest possible time in order to minimize the ischemic time: the greatest benefit is accrued if reperfusion can be achieved within the first 3 hours.[3] For many years research has focused on establishing whether Primary Percutaneous Coronary Intervention (PCI) or administration of thrombolytic drugs is the better initial strategy. A review of 23 randomized trials enrolling 7 739 patients has established the superiority of Primary PCI in minimizing death, reinfarction, and stroke.[4] Primary PCI results in better arterial patency rates[5] and avoids the life-threatening complication of intracranial haemorrhage associated with thrombolytic drugs.[1]

There are major logistical limitations that limit the applicability of primary PCI in the South African context. Facilities that are equipped for primary PCI are limited in number, and distances from community hospitals are often great. Best results are achieved when a primary PCI facility is available 24 hours a day, 365 days a year,[6] and this is not achievable in South Africa due to limited resources. As a result, most South Africans with STEMI, who present to hospital within the therapeutic window of opportunity will receive a thrombolytic agent rather than primary PCI. The question as to whether lytic therapy can be improved by adjunctive immediate PCI and the management of failed thrombolytic therapy are important issues in South Africa.

There are 3 different time-related PCI strategies that can be applied after initiation of fibrinolysis: facilitated PCI involves the administration of fibrinolytic therapy with a view to improving flow in the infarct-related artery before planned immediate PCI. Rescue PCI is PCI performed when there is failure of fibrinolysis, usually indicated by ongoing chest pain and/or the absence of ST-segment resolution at 60 to 90 minutes after initiation of fibrinolytic therapy. The third strategy is that of systematic early PCI, 24 hours after administration of fibrinolysis irrespective of the latter's success, rather than delayed and/or ischemia-driven PCI.

FACILITATED PCI

Facilitated PCI is a strategy in which a patient with evolving, acute ST-elevation myocardial infarction is given a pharmacological agent, followed by immediate PCI, with a view to achieving earlier arterial patency. This has been an attractive concept throughout the world,

and results of randomized trials were eagerly awaited. The patient would theoretically receive the benefit of both therapies.

The AHA, ACC update on management guidelines for ST-elevation MI[7] points out that facilitated PCI should be differentiated from primary PCI without fibrinolytic therapy, from primary PCI with a GPIIb/IIIa inhibitor started at the time of PCI, from early or delayed PCI after successful fibrinolytic therapy, and from rescue PCI after unsuccessful fibrinolytic therapy.

Several early randomized, placebo-controlled trials demonstrated a 40% to 60% reduction in a 30-day composite ischemic end point (death, myocardial reinfarction and urgent target vessel revascularization [TVR]) with abciximab in this setting. The benefit was primarily driven by a reduction in the rates of reinfarction and urgent TVR. No individual trial observed a statistically significant reduction in 30-day mortality. These trials gave momentum to the facilitated PCI concept and led to larger trials assessing both GPIIb/IIIa inhibitors and thrombolytics in facilitated PCI.[8,9,10,11]

Indeed, facilitated PCI does achieve better patency rates and better TIMI 3 flow rates than does primary PCI, but this attractive strategy has ultimately failed to deliver on its theoretical promise. Keely et al. published a meta-analysis of 17 randomized trials comparing facilitated and primary angioplasty in 4 504 patients,[12] including the large 1 667 patient ASSENT-4 trial.[13] The pharmacological agent was thrombolytic therapy alone in six trials, platelet glycoprotein IIb/IIIa (GPIIb/IIIa) antagonists alone in nine trials, and the combination of reduced dose thrombolysis (usually 50%) and GPIIb/IIIa antagonists in two trials. Facilitated PCI resulted in an increase in mortality, recurrent ischemia, major bleeding and stroke. Thrombolytic therapy was identified as the culprit for adverse outcomes (either without or with GPIIb/IIIa antagonists). GPIIb/IIIa antagonists alone did not worsen outcomes but were not beneficial. The ASSENT-4 PCI trial[14] was terminated prematurely because of a higher in-hospital mortality rate in the facilitated PCI group (6% vs. 3%; p=0.01).

Possible explanations for these findings are examined in an editorial accompanying the publication of the ASSENT-4 trial by Stone and Gersh.[15] Door-to-balloon times in experienced centres are now similar to the time it takes for a lytic to be administered and for the additional 60 minutes required for its effect. The lytic may therefore not be achieving its theoretical goal in advance of mechanical reperfusion. Also, the addition of lytic increases bleeding, which is in and of itself associated with mortality.[16] Increased myocardial haemorrhage can offset the myocardial salvage from reperfusion and can promote rupture. Finally, thrombolytic induced platelet activation may be responsible for increased reinfarction and emergency repeat revascularization.

It would appear that facilitated PCI has all but had the door closed upon it. In the AHA, ACC update on management guidelines for ST-elevation MI,[7] facilitated PCI remains a possible option in a patient at a low risk of bleeding, with a high-risk infarct, and an anticipated very long time for transportation to a PCI centre. The ASSENT-4 trial, however, failed to suggest that such patients may benefit from a facilitated approach.

Dr Steve Ellis presented the results of the FINESSE Trial at the European Society of Cardiology Congress in Vienna, Austria in 2007. The Trial randomized 2 452 patients to facilitated PCI with either up-front abciximab plus half dose reteplase or up-front abciximab alone followed by PCI versus primary PCI alone. The study was terminated prematurely due to difficulty with enrolment. There were no differences between groups in the primary endpoint of death or complications of MI (heart failure, arrhythmias or cardiogenic shock), and there was an increased incidence of bleeding in both facilitated groups. Thus thrombolytics cannot be recommended as pre-treatment for patients with STEMI in whom primary PCI is the planned treatment.

A meta-analysis of placebo-controlled abciximab trials for ST-segment elevation myocardial infarction (STEMI) did demonstrate a moderate reduction in mortality at 30 days (2.4% vs. 3.4%, p = 0.047) and at 6 to 12 months (4.4% vs. 6.2%, p = 0.01) among those receiving abciximab during primary angioplasty. In a subsequent analysis of this combined dataset, the mortality benefit was shown to be proportional to the baseline risk; the higher the risk, the higher the benefit from abciximab.[17]

The data for GPIIb/IIIa antagonists is conflicting and there is not enough evidence to suggest routine pre-treatment with GPIIb/IIIa antagonists, but in higher risk patients, particularly in diabetics, and when there is

visible thrombus, GPIIb/IIIa antagonists can be considered at the time of PCI. As mentioned earlier, this is not the same as facilitated PCI (i.e. pre-treatment) where they appear not to be beneficial.

How should community hospitals treat STEMI patients? Transfer of patients to an interventional hospital, in favour of thrombolysis, is advantageous if the time from arrival at the first hospital to balloon dilatation at the destination hospital is under 2 hours.[18,19] Therefore, most patients presenting inside the 3-hour window, to a community hospital without PCI facilities, should still receive thrombolytic therapy. We await the outcomes of trials investigating the effects of withholding thrombolytic therapy when transfer times to an interventional facility are longer.

RESCUE PCI

Thrombolysis is not universally successful. The rate of successful reperfusion (based on angiography at 90 minutes post-thrombolysis) is no better than 50%. The 2004 AHA, ACC STEMI Guidelines recommend urgent coronary angiography with intent to perform PCI, regardless of the time since initiation of fibrinolytic therapy, in certain patients: cardiogenic shock, severe congestive heart failure / pulmonary oedema or haemodynamically compromising ventricular arrhythmias.[20] These cases do not fall into the category of rescue PCI. Rescue PCI represents a strategy of PCI in patients who do not have the above clinical instability, but in whom there is the clinical suspicion of failed thrombolysis. Failure of resolution of chest pain is not a reliable gauge of reperfusion. Clinical assessment of reperfusion is best based on the degree of ST-segment resolution on the 12-lead ECG. If there is less than 50% ST-segment resolution in the lead showing the greatest degree of ST-segment elevation at presentation, fibrinolytic therapy has likely failed to produce reperfusion.[21]

The treatment for failed thrombolysis has included conservative management, repeat dose thrombolysis, and rescue PCI. The treatment of choice has been uncertain. Two recently published trials dealing with this subject are the REACT trial and the MERLIN trial.

REACT demonstrated that rescue PCI is associated with an improvement in the combined end point of death, reinfarction, stroke, or severe heart failure, when compared with repeat fibrinolysis or conservative management.[22] The end point was driven mainly by a difference in reinfarction: there was no difference in mortality. MERLIN also did not demonstrate a difference in mortality when rescue PCI was compared with conservative therapy, but rescue PCI did reduce recurrent ischemia.[23] In both trials, bleeding, a predictor of adverse outcome, was increased.[22,23]

In order to obtain better guidance in treating this difficult problem of failed thrombolysis, Wijeysundera and colleagues have published a meta-analysis of 8 randomized trials, enrolling 1 177 patients, including REACT and MERLIN.[21] Six trials randomized 908 patients to rescue PCI vs. conservative therapy and 3 trials randomized 410 patients to repeat fibrinolysis or conservative therapy.

Rescue PCI was not associated with a significant improvement in mortality compared with conservative therapy. Heart failure and reinfarction were, however, significantly reduced with rescue PCI. The composite of death, heart failure and reinfarction was significantly reduced by rescue PCI ($p<0.001$, number needed to treat = 9). Stroke was significantly higher with rescue PCI (3.4% vs. 0.7%). Interestingly, most strokes were thrombo-embolic and not haemorrhagic, and numbers were small. There was no difference in major bleeding but minor bleeding was considerably higher with rescue PCI (16.6% vs. 3.6%). The increased bleeding suggests that adjustments in antithrombotic medication dosing are required in order to improve safety.

The strategy of repeat fibrinolytic therapy for failed thrombolysis did not achieve a reduction in mortality or reinfarction. There was an increase in minor, but not major, bleeding. Stroke data was inadequate.

Another meta-analysis by Collet[24] evaluated 5 trials (920 patients). The odds ratios for death or reinfarction with rescue angioplasty versus conservative approach within the first 30 days was 0.60 in favour of rescue PCI, $p = 0.012$.

These data support the use of rescue PCI, over conservative treatment, for failed fibrinolysis in STEMI. In contrast, repeat fibrinolysis cannot be recommended based on the available evidence.

The updated AHA, ACC STEMI guidelines make the point that low risk patients may be treated conservatively. Patients with symptom resolution and improving ST-segment elevation (but with less than 50% resolution), or inferior MI localized to 3 ECG leads, probably should

not be referred for angiography. The guidelines also highlight that the findings at angiography are important: it is doubtful that PCI of a branch artery (diagonal or obtuse marginal branch) will change the prognosis in the absence of high-risk clinical criteria.

SYSTEMATIC EARLY PCI

In the Collet meta-analysis, six randomized trials were identified for the comparison of systematic, early catheterization, versus delayed and/or ischemia-guided catheterization after fibrinolysis (1 508 patients). Patients underwent systematic PCI within 24 hours (mostly <6h) after thrombolysis. The overall analysis showed a non-significant trend toward a reduction of death or myocardial infarction in the systematic early PCI group, without excess bleeding.[24] While systematic early PCI is a recommendation in the ESC guidelines,[25] there is little data upon which to make recommendations for adoption of such a strategy, but the meta-analysis indicates that early PCI after fibrinolysis is probably safe.

Mechanical methods to facilitate procedural success in STEMI PCI

A successful PCI procedure in the epicardial infarct-related artery is not equivalent to the restoration of myocardial perfusion at the cardiac microcirculation level. Distal embolization, slow-flow and no-flow phenomena occur in 30% of patients.[16] Following primary PCI, reperfusion of the microcirculation is assessed by the myocardial blush grade (MBG). A normal MBG 3 is seen in only one-third of patients, with two-thirds having impaired myocardial reperfusion (MBG 0-226). Patients with impaired microvascular reperfusion have increased early and late mortality and heart failure.[27] Distal embolization is an important player in failed microvascular reperfusion, while other mechanisms include vasospasm and edema of the surrounding myocardium.[28] Embolic material can include thrombus, plaque fragments, lipids, platelet clumps and neutrophils.

Thrombectomy and distal protection are attractive modalities as adjuncts to primary PCI because of their theoretical ability to minimize distal embolisation.

Distal protection devices

Distal protection devices have proven to be of value in reducing distal embolization in saphenous vein graft PCI.[29,30] Distal protection showed early promise, but the EMERALD[31] trial did not demonstrate a benefit for balloon distal protection in terms of ST-segment resolution or infarct size at 30 days. The PROMISE[32] trial, using a filter device, was also negative. In the PREMIAR[33] trial, the use of another filter-based distal protection device showed no advantage in improvement of myocardial reperfusion. Thus far a total of six trials with embolic-protection devices have shown no benefit of distal protection in the management of acute PCI for ST-elevation MI.

An area of possible further research for embolic protection remains the concept of proximal, or flow reversal protection, in which protection can be established before crossing the lesion with a guide wire.

Thrombectomy

A number of thrombectomy devices have been studied. The principles involved in device design varies from rheolytic thrombectomy (AngioJet - Possis Medical, Minneapolis, MN, USA), to a number of easy to use, cheaper aspiration devices. Early small studies showed improved ST-segmentation resolution in STEMI patients with a large thrombus burden treated with thrombectomy during primary PCI. However, the AIMI trial of AngioJet thrombectomy, in all-comers with AMI, did not show benefit for thrombectomy over conventional therapy.[34] Visible thrombus was not required for inclusion and critics of this trial cite the low thrombus burden as a major limitation. The ongoing JETSTENT trial, using the AngioJet device, will hopefully help to answer whether thrombectomy is helpful in patients with a large clot burden.

Of 10 trials evaluating thrombectomy devices, eight, mostly smaller studies, have shown some improvement in myocardial perfusion, while two bigger trials have shown no benefit. One trial demonstrated possible harm from thrombectomy with an increase in infarct size compared to controls.[30] Interestingly, GPIIb/IIIa inhibitors have not been shown to impact on these outcomes.[36,37] A recent trial of the cheaper strategy of thrombus aspiration has shown potential benefit of simple aspiration,[38] but this will require confirmation in a larger trial.

The following can be deduced from the data currently available: thrombectomy cannot be recommended for routine use in primary PCI, as most patients do not benefit. The role for thrombectomy, most likely, lies in the patient with a large thrombus burden. In such cases PCI is technically very difficult and thrombectomy makes the procedure less

complicated to perform. The Jetstent trial will, hopefully, shed light on the role of thrombus extraction in this specific subgroup of AMI patients.

CONCLUSIONS

It is now well established that primary PCI is a superior strategy for treating acute STEMI as an initial strategy within the first 6 hours from symptom onset. Facilitated PCI is a strategy that is of no benefit and neither GPIIbIIIa inhibitors nor thrombolytics are recommended as upfront treatment before planned PCI.

Primary PCI is not widely applicable in South Africa and therefore most patients with ST-elevation MI will receive thrombolysis. When thrombolysis fails, as indicated by failure of ST-segment elevation to resolve within 90 minutes, rescue PCI is recommended.

Early PCI within 24 hours of lytic therapy is not of proven benefit but appears to be safe.

In patients with ST-elevation MI who undergo primary PCI, thrombectomy may be a useful adjunct in the presence of a large thrombus burden but is of no benefit in other situations. Distal protection does not seem to have a role in acute myocardial infarction.

An important message from the facilitated PCI, thrombectomy and distal protection trials is that many therapeutic concepts that appear intuitively logical don't stand up to the rigorous scrutiny of randomized trials.

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