Randomized Controlled Trial Of Late Coronary Stenting Of The Infarct Related Vessel In Asymptomatic Patients After Myocardial Infarction

Monvadi Barbara Srichai

A. Study purpose and rationale

Following acute myocardial infarction, patients with a patent infarct-related vessel have a favorable long term prognosis compared with those whose vessel remains occluded (1-2). Sustained patency of the infarct-related vessel is associated with decreased infarct expansion, improved left ventricular remodeling, preservation of cardiac function and reduction in electrical instability (3-7). Early thrombolytic therapy when feasible will often fail to produce early reperfusion approximately 25% of the time (8). In addition, several patients often present late in the course of their myocardial infarction, when reperfusion can no longer achieve myocardial salvage (9-10).

A number of experimental and clinical studies support the concept that reperfusion of occluded vessels beyond the time frame for myocardial salvage and up to 3 months post myocardial infarction prevents left ventricular dilatation (3,11-15). Potential mechanisms of benefit include improved infarct healing and scar formation, maintenance of structural integrity via an open filled coronary vascular bed, and perfusion of hibernating myocardium (16). Studies thus far have largely been nonrandomized, observational trials. This study aims to assess the effect of late PTCA with coronary stent placement in an occluded or stenotic infarct-related artery on left ventricular remodeling post myocardial infarction. Secondary analyses will include the effects of the presence of myocardial viability prior to intervention and infaret location on long term left ventricular remodeling.

B. Study design

This is a prospective randomized, intervention versus medical therapy study to evaluate the effect of late coronary stent placement in asymptomatic patients with an occluded or stenotic (>70%) infarct related vessel up to 2 weeks after myocardial infarction. Patients eligible for participation will undergo baseline ECG, echocardiography, stress testing, and metabolic PET scanning evaluation prior to randomization. Patients will be stratified by infarct location (anterior versus other) and presence of viability in the infareted region. Patients who remain asymptomatic and who do not show evidence of severe ischemia on low level stress testing will then undergo cardiac catheterization within 2 weeks post myocardial infarction. Patients with evidence of an occluded or stenotic infarct related vessel will then be randomized to receive immediate coronary angioplasty with stent placement or conventional medical therapy. Exclusion from randomization includes: 1) widely patent infarct-related vessel, 2) stenosis of the left main artery of more than 50% or the equivalent of significant stenoses in 2 or more vessels supplying at least 40% of the LV myocardium, and 3) severe diffuse multilesional infarct vessel disease. Randomization will be carried out within each stratification group. Patients will have a follow-up echocardiogram at 6 months. Please see Figure I for trial design.

The primary analysis will be an intention to treat comparison of the relative changes in left ventricular volumes and ejection fraction between the two treatment arms 6 months after randomization. A secondary analysis of the primary endpoint will be a subgroup analysis of presence or absence of viability and infarct location and their effects on the relative changes in left ventricular volumes and ejection fraction.

Based on an alpha value of 0.05 and power of 0.80 with an approximated standard deviation of 15 between the percent change of volume over the 6 months, approximately 45 patients will be needed in each treatment arm to detect a 10% difference between the two treatment- groups. Up to 120 patients will

be recruited for participation from Columbia-Presbyterian Medical Center and the Allen Pavilion. It is estimated that out of the 120 patients with an uneventful post MI course 80% will have evidence of an occluded or stenotic infarct related artery.

C. Study subjects

Any patient suffering from a recent myocardial infarction is eligible for participation. Criteria for the initial diagnosis of recent myocardial infarction are a minimum of a 2mm ST segment elevation in at least two leads, followed by the occurrence of Q waves in the same leads and elevation of total creatine kinase level to at least twice the upper limit of normal, and a positive creatine kinase-MB band. Exclusion criteria include non-Q wave infaretion, presentation after I week post M1, previous coronary artery bypass surgery, cardiogenic shock defined as systolic blood pressure below 80mmHg. congestive heart failure at admission, associated valvular heart disease, known dilated or hypertrophic cardiomyopathy, post-infarction ischemia or reinfarction. Patients who receive primary PTCA prior to participation will also be excluded from the study.

Any therapy required by a patient's condition was left to the discretion of the attending, physician involved in the patient's care, including beta-blocking agents, ACE inhibitors, anticoagulants and aspirin. Thrombolytic therapy could have been administered to any patient free of contraindications.

D. Recruitment of subjects

Patients who present to the coronary care unit or medical intensive care unit with new onset myocardial infarction will be identified for possible participation. Patients who have an uncomplicated post MI course and who meet with study criteria will be approached for possible participation once they are on the cardiac ward.

E. Study procedures

All patients will undergo baseline studies including ECG, echocardiography, low level stress testing, and PET scanning prior to cardiac catheterization and within I week post MI.

Two dimensional echocardiograms of the left ventricle will be obtained using a standard HP or compatible machine and recorded on VHS videotapes. Apical two and four chamber views will be used for measurement of LV volumes and ejection fraction.

Echocardiograms will be analyzed by two independent readers in a blinded manner. The measurements will be compared and averaged. Any large discrepancies between the measurements will be repeated and re-evaluated. If large discrepancies remain then both readers will collaborate and discuss the differences. A new measurement will then be performed upon resolution of discrepancies. The volumes will be normalized for body surface area.

Low level exercise or dobutamine stress echocardiography will be performed for identification of patients with severe inducible ischemia. These patients will be excluded from further participation as prior studies have shown this subgroup to benefit from revascularization. Low level exercise testing will be performed using the modified Bruce protocol. Severe ischemia during testing is defined as angina symptoms, ST segment depression < 2mm, ST segment elevation > 1 mm in leads without Q waves or inability to complete stage I of a standard Bruce protocol, failure to achieve 3 or 4 METS or exertional hypotension (17). Patients with abnormal baseline ECG's will undergo dobutamine echocardiography. Patients who develop chest pain or wall motion abnormalities in multiple territories on echocardiography will be excluded from further participation.

PET imaging of the heart with 18F-FDG has been proven a valuable tool and superior to other imaging modalities for the detection of viable myocardium or ischemically injured myocardium (18). Patients who demonstrate relative or absolute increases (relative to normal myocardium) in FDG uptake

in regions of the myocardium that correspond to the infarct zone will be judged to have viable myocardium in the region of interest.

Upon qualification for study participation and after stratification patients will undergo cardiac catheterization within 2 weeks post MI. Coronary angiograms of multiple views of the left and right coronary systems will be obtained. The infarct related artery as determined by ECG and echocardiography will be assessed for patency. Patients with occluded or stenotic arteries will be eligible for randomization to PTCA with coronary stent placement or medical therapy. Coronary stenting will be employed with standard devices regardless of primary PTCA result as they have been shown to result in improved long term angiographic and clinical outcomes (19).

F. Confidentiality of study data

Once a patient agrees to participate in the study a unique coding number will be assigned to the patient for future reference.

G. Location of the study

Patients will be identified on the cardiac ward. Appropriate studies will be performed prior to the patient's discharge date. Patients at the Allen Pavilion will be transferred to CPMC Milstein Hospital for completion of appropriate studies.

Potential risks and benefits

All procedures performed in this study are commonly performed for clinical indications, with well-defined low risks. The risk of coronary anglography and PTCA will be minimized by the selection of experienced operators. Patients who participate in this study will receive the standard of care with close follow-up.

H. Alternative therapies

Presently the standard practice for patient's after an uncomplicated MI includes risk stratification followed by intervention if indicated or medical management with diet and behavioral modification. Alternatively, some physicians elect for more aggressive interventions with revascularization in patients with low risk post MI course, though such measures have not been proved to be effective.

I. References

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