A prospective, randomized clinical trial of coronary artery bypass graft surgery vs. coronary artery bypass graft surgery plus mitral valve surgery in patients with moderate ischemic mitral regurgitation as a complication of coronary artery disease

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A. Study Purpose and Rationale

Ischemic mitral regurgitation (MR) is regurgitation that occurs despite structurally normal valves as a consequence of left ventricular remodeling in ischemic heart disease. Ischemic MR occurs in approximately 20% of patients with coronary artery disease (1). In a long term study of patients with coronary artery disease, Grigioni et al showed that the presence of ischemic MR is associated with excess mortality, and the mortality risk is related directly to the severity of ischemic MR (2).

The appropriate therapy for patients with CAD complicated by MR is controversial. Revascularization via coronary artery bypass graft surgery (CABG) has been shown to improve MR in patients undergoing CABG alone, but some argue a more aggressive management strategy specifically targeting the mitral valve should be considered. For the two extremes in severity, there is little controversy. CABG + mitral valve repair or replacement is standard of care in patients with severe MR given the poor long term prognosis if MR persists. CABG alone suffices for patients with mild MR. However, the role of mitral valve surgery (MVS) in patients with moderate ischemic MR remains unclear (8, 10). The uncertainty lies in balancing the known long term risks of chronic mitral regurgitation with the risks and benefits associated with operative repair (5).

A case-control study by Di Donato et al showed that repair of the mitral valve at the time of CABG leads to a better clinical status due to an improved hemodynamic profile (NYHA class, LV dimensions, ejection fraction) in a homogeneous series of 60 patients with moderate ischemic MR (4). However, Tolis et al looked at revascularization alone and concluded that CABG alone suffices given a significant decrease in degree of MR from mild-moderate to trace MR (1.73 to 0.54, $p < 0.05$) and a 65% survival three years (10). Numerous prospective studies have looked at CABG alone vs. CABG + MVS, but there is no consensus on the best management strategy for patients with moderate ischemic MR. A prospective, randomized trial in now needed to clarify the role of CABG alone vs. CABG plus adjunctive MVS in treating patients with moderate ischemic MR.

B. Study Design and Statistical Analysis

This is a prospective, randomized trial of CABG vs. CABG + MVS in patients with moderate ischemic mitral regurgitation.

Patients who are scheduled for CABG in the Division of Cardiothoracic Surgery Columbia Presbyterian Medical Center (CPMC) will be invited to enroll. When surgeons schedule a patient for CABG, surgeons will ascertain from the patient that he/she is willing to discuss the study with the research team. The research team will then approach the patient about recruitment. After giving consent, patients will undergo a screening standard transthoracic echocardiogram. According to their results, patients who meet the inclusion criteria listed below will be asked to continue in the study. The research team will be responsible for consulting with the cardiac surgeon to confirm that the potential subject is a good candidate for randomization.

Patients will then be randomized in a 1:1 ratio to two study groups, one group undergoing CABG alone and one group undergoing CABG + MVS. Randomization envelops will be provided to the attending surgeon by a data coordinating center, and the type of mitral valve repair will be at the discretion of the attending surgeon. The randomization will be masked to the investigational team until all data is collected and ready to be analyzed.

Our goal for enrollment will be 467 subjects per study group based on the chi-squared test on proportions to achieve 80% power and a type I error of 0.05. Samples size calculations are based on a primary outcome of total cardiac events (cardiac death + cardiac rehospitalizations) at 3 years, using data from previous observational studies of CABG vs. CABG + MVS which showed a total cardiac event rate of 45% in the CABG group and 35% in the CABG + MVS group. Sample size calculations account for a 20% dropout rate, which should be anticipated due to cardiac and non-cardiac death during the study period.

The primary outcome in this study will be total cardiac events, which includes cardiac death and cardiac rehospitalization due to MI, CHF, or arrhythmia.

Secondary outcomes will include NYHA class, echocardiography outcomes, (severity of mitral regurgitation, LV ejection fraction), operative mortality, short term mortality (<30 days post-op), long term mortality (>30 days post-op), cardiac rehospitalizations, and cardiac death.

The primary end point will be examined using the chi-square test on proportions. In addition, the secondary end points of operative mortality, short term mortality, long term mortality, cardiac rehospitalization, and cardiac death will be examined using the chi-square test on proportions. Kaplan-Meier survival curves will be used to analyze rehospitalizations, long term mortality, cardiac death, and total cardiac events over time. The NYHA class and echocardiography outcomes will be assessed using the student's unpaired t-test.

C. Study Procedure

The likely duration of the study will be 8 years, with an anticipated duration of participation of 3 years for each subject. Baseline interview and echocardiogram will be performed within 1 week prior to surgery. Surgery will then be performed by the attending surgeon. Patients will have follow-up interview and echocardiography at 3 months, 6 months, 1 year, and 3 years. In addition, all patients will receive standard post-procedure care as judged appropriate by the principle investigator and/or cardiac surgeon.

D. Study Drugs:

This study will no utilize investigational drugs.

E. Medical devices:

This study will not utilize investigational devices.

F. Study Questionnaires

There is no study questionnaire associated with this study.

G. Study Subjects

Inclusion:
- patients scheduled for CABG (excluding emergent revascularization)
- EF <50% at baseline echocardiogram
- Moderate MR at baseline echo – effect regurgitant orifice (ERO) 0.25 - 0.4 cm^2

Exclusion:
- technically inadequate echocardiogram

- structurally abnormal mitral valve
- severe MR
- mild MR
- other significant valvular disease

H. Recrutiment of Subjects

Patients who are scheduled for CABG in the Division of Cardiothoracic Surgery Columbia Presbyterian Medical Center (CPMC) will be invited to enroll. When surgeons schedule a patient for CABG, surgeons will ascertain from the patient that he/she is willing to discuss the study with the research team. The research team will then approach the patient about recruitment.

I. Confidentiality of Data

Subject confidentiality will be maintained throughout the clinical study by assigning a unique subject identification number at identifies all data reported for each subject. Confidentiality of patient data will be protected by the use of a locked cabinet in the research unit and limited access storage to electronic data.

J. Potential Conflict of Interest

There is no potential conflict of interest.

K. Location of Study

This study will take place at Columbia Presbyterian Medical Center.

L. Potential risks

CABG:
Risks of CABG include, but are not limited to, the following:

- Myocardial infarction - 5% of surgeries
- Stroke/transient ischemic attack – 2.8% of surgeries although the risk is greatest in those over 70 years old.
- DVT/pulmonary embolus
- Death – 3-4% of patients
- Deep wound infection – 1-4% of surgeries
- Re-operation within 24 hrs – 5.6%
- Hemorrhage requiring transfusion – 1.9%
- Arrhythmia
- Endocarditis
- Sepsis
- Pericardial effusion/tamponade
- Anesthetic reaction

CABG + MVS:
Risks of CABG + MVS are the same as those of CABG alone. Risk of these adverse events may or may not be greater with combined CABG + MVS given increased operative time, increased bypass pump time, and increased exposure to anesthesia. Operative death for CABG + MVS is reported to be 9-15%. Additional risk includes mitral valve repair failure, resulting in persistent MR.

Echocardiography:
There are no risks associated with transthoracic echocardiography.

M. Potential benefits

The potential benefits of CABG + MVS are related to the potential reduction in MR. Potential benefits include, but may not be limited to, the following:

- Elimination or reduction in MR
- Improved LV function
- Improved NYHA functional class
- Decreased cardiac rehospitalization rate
- Improved long term survival

N. Alternative therapies

If the patient chooses not to participate in this study, alternative therapies for moderate ischemic MR include the current clinically available medical and surgical treatments. These options include: 1) CABG alone, 2) CABG + mitral valve repair, 3) CABG + mitral valve replacement, or 4) medical management. The decision not to participate in this study will not affect the patient's previously scheduled CABG.

O. Compensation to Subjects

Patients will not receive any payment or other compensation for participating in this study.

P. Cost to Subjects

There will be no additional costs to the patient as a result of participating in this study.

Q. Minors in Research

Minors will not be enrolled in this study.

R. Radiation or Radioactive Substance

Patients will not be exposed to additional radiation or radioactive substances as a part of their participation in this study.

S. References

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