A Randomized Clinical Study To Compare The Intra-Aortic Balloon Pump To A Percutaneous Left Atrial-To-Femoral Arterial Bypass Device For Treatment Of Cardiogenic Shock Following Acute Myocardial Infarction.

Rhondalyn C. McLean

A. Study Purpose and Rationale

Design:

This will be a prospective randomized study designed to compare the efficacy of the intra-aortic balloon pump versus a ventricular assist device in providing short term circulatory support to patients with persistent cardiogenic shock secondary to acute myocardial infarction.

Rationale:

Cardiogenic Shock and Left Ventricular Support

Cardiogenic shock (CGS) is associated with a very high mortality due to inadequate end organ perfusion. Though many advances in medical and interventional therapies have been made for the treatment of the complications occurring after acute myocardial infarction, cardiogenic shock remains the most common cause of death in these patients. After an acute myocardial infarction the heart muscle may require several days to recover the ability to pump well. It is during this time period that the patient is at most risk for the development of circulatory collapse. Scientists and clinicians have been challenged to find a solution for this significant medical problem.

Currently the intra-aortic balloon pump (IABP) is the recommended treatment of choice for cardiogenic shock after revascularization. This device increases the mean arterial pressure, reduces cardiac afterload and augments cardiac output and coronary blood flow. However patients presenting with CGS following acute myocardial infarction have an extremely poor prognosis with a reported mortality of 30 to 80% despite aggressive pharmacological therapy and use of the intra-aortic balloon pump (IABP). Analysis of data from the GUSTO-I Study showed that though there was no difference in 30 day mortality in the group who received an IABP versus those who did not, there was a significantly longer median time to death in the IABP patients (2.8 days vs. 72 hours, p=.0002). Also noted was that 50% of all mortality in the non-IABP group occurred within the first 8 hours whereas only 23% of the IABP group died within the first 8 hours after randomization.

There is evidence that an intra-aortic counterpulsation device might have an effect on dilation of the coronary vessels, A 1999 Japanese study using an animal model showed that effective coronary flow pulsation dilates epicardial coronary arterioles and its vasodilatory effect is mediated by enclothelial nitric oxide. Thus the actual mechanism and placement of the device may offer protection against ongoing ischernia not only by helping to unload the work of the left ventricle but also by increasing relaxation of the coronary arteries and subsequent increase in blood flow.

Because there is such a high mortality with CGS even in the setting of an IABP, a new therapeutic intervention that is capable of achieving effective circulatory support to stabilize CGS patients would be beneficial. In 2001 investigators in Germany implanted a percutaneous left ventricular assist device in 18 patients who were in cardiogenic shock resulting from an acute myocardial infarction. The authors showed that after implantation of the device there was statistical 'improvement in cardiac index

(1.7 ± 0.3 L/min/M2 vs. 2.4 ± 0.6 L/min/m', p<0.001) and in mean arterial pressure (63 ± 8 mmHg vs. 80 ± 9 mmHg, p<0.001). However, one-half of all patients died within a 30 day period following explantation of the device. This study lacked a control group and enrolled only a small number of subjects.

The ventricular assist device acts by unloading the left ventricle and allowing for recovery of stunned myocardium after ischemia. The IABP should work in a similar manner but have the added benefit of being able to increase coronary artery perfusion thus resulting in better cardiac recovery and output. We hypothesize that patients who suffer from cardiogenic shock secondary to myocardial infarction will in the short term do clinically better with the IABP vs. the left ventricular assist device. We will measure the change in cardiac index, mean arterial pressure and survival at 3 days for the two groups.

B. Study Design and Statistical Analysis

This is a study in which 206 patients at up to 20 national and international sites will be randomized into one of two groups with each treatment arm having a probability of 0.5. Outcome measures will include hemodynamic improvement, survival and safety outcome measures (e.g., bleeding complications and distal limb ischemia). The primary endpoint as measured by the cardiac index and mean arterial blood pressure will be hemodynamic improvement at four hours after device implantation. The secondary endpoint of this study shall be survival without permanent neurological dysfunction at 3 days after device implantation.

Long-term follow-up will consist of an electrocardiogram performed at 6 weeks and contact at 6 and 12 months to determine whether any major adverse cardiac events have occurred. Additionally those patients in the left ventricular assist device group will return at 3 months for an echocardiogram.

Sample Size

The proposed sample size is 206 randomized patients in this 2-arm trial (103 in each arm). This sample size is based on a simple analysis of the proportion of patients in each arm that survive at 3 days. It is based on the following power analysis:

Efficacy: 3-day mortality of the IABP is 30%.
3-day mortality of the TandemHeart System is 50%
Power of 80%
Alpha error of 5%
Calculated sample size per arm is 103

In addition, this sample size will allow for comparison of the primary outcomes as measured by change in cardiac index and mean arterial pressure.

Statistical *Analysis*

The primary and secondary endpoints will be analyzed on an intent-to-treat basis. Patients will therefore be analyzed according to the randomized treatment regardless of the subsequent sequence of events. All clinically relevant baseline variables will be tabulated and compared between the two treatment arms. To detect differences in patient characteristics between the randomized treatment assignment groups, the means of continuous variables will be compared by *t* tests. Dichotomous variables will be compared by χ^2 tests.

C. Medical Devices

IABP

This device has been approved for several uses including cardiogenic shock, bridge to revascularization, refractory angina, high-risk revascularization procedures and as a bridge to cardiac transplant. Under fluoroscopic guidance the aorta is accessed via the femoral artery. A guide-wire is placed and a sheath containing the balloon catheter is inserted over the guide-wire. The balloon is

advanced until the proximal tip is 1 cm below the left subclavian artery. As systole begins the balloon which is connected to a helium source is deflated. This creates a negative pressure in the descending portion of the aorta leading to increased forward flow. When the balloon is inflated during diastole, blood is pushed towards the heart resulting in increased coronary perfusion pressures.

Tandemheart ™ pVAD System

This device is investigational. CardiacAssist, Inc. has developed a new short term left ventricular assist device called the TandemHeart pVAD System. This device is placed under fluoroscopic or trans-esophageal echocardiographic (TEE) guidance in a catheterization lab setting and is designed to unload the left ventricle and provide short-term circulatory support for CGS patients. The TandemHeart pVAD System is a left ventricular assist device that can be inserted percutaneously in the cardiac catheterization lab. A trans-septal cannula, inserted through the femoral vein and advanced across the intra-atrial septum into the left atrium, supplies blood from the left atrium to a small centrifugal pump. Oxygenated blood is withdrawn from the left atrium into the housing of the pump and propelled by the impeller out through the outflow port of the pump. The blood is returned to one or both femoral arteries via arterial cannula(e).

D. Study Procedures

Following randomization, subjects randomized to the treatment group will undergo TandemHeart device placement, Subjects randomized to the control group will undergo IABP placement.

E. Study Drug

Not applicable.

F. Study Questionnaires

There are no questionnaires for this study.

G. Study Subjects

***Inclusion* Criteria**

Patient or legal representative willing to provide Informed Consent
Age ≥ 18 years old
Patient must have had a myocardial infarction as defined as:

- Chest pain for > 20 minutes but < 6 hours accompanied by
  - >0. 1 mm ST segment in two or more limb leads or
  - >0.2mm ST segment elevation in two or more contiguous precordial leads or
  - New LBBB

Patient has cardiogenic shock for no longer than 24 hours, defined as:

- MAP ≤ 80 mmHg or the need for inotropic support to maintain MAP > 80 mmHg
- Cl < 2.2 L/min/M^2
- PCWP ≥ 15 mmHg
- Evidence of end-organ hypoperfusion with at least one of the following
- Urine output <0.5 ml/kg/hr
- Cold extremities
- Altered mental status

Patient must have cardiogenic shock < 36 hours after myocardial infarction.

Patient has persistent, medically refractory cardiogenic shock defined as the patient meeting the criteria for cardiogenic shock, and remaining in persistent cardiogenic shock despite conventional therapy, for at least 1 hour but not more than 24 hours despite appropriate medical therapy with at least:

- Inotropes (e.g. dobutamine ≥ 10 mcg/kg/min, milrinone ≥ 0.5 mcg/kg/min, etc.)

Exclusion **Criteria**

1. Isolated right heart failure
2. Other causes of cardiogenic shock
3. Contraindication for systemic anticoagulation
4. Severe peripheral vascular disease (PVD) as evidenced by lack of palpable or Doppler-able distal pulses or a history of femoral, iliac or aortic aneurysms.
5. Life expectancy less than 6 months due to non-cardiac condition
6. Clinically significant aortic valve regurgitation, 2+ or greater
7. Significant neurological deficit or CVA (cerebrovascular accident) within past 6 months

H. Recruitment of Subjects

Patients admitted with evidence of cardiogenic shock will have their clinical history reviewed by a member of the research team. If all clinical inclusion criteria are met and no clinical exclusion criteria are present, the patient will be eligible. The study coordinator will explain the study carefully or one of the study investigators and all questions will be answered. Informed consent from the patient or authorized representative will be obtained.

I. Confidentiality of Study Data

Confidentiality of medical records will be maintained. Assigning medical records a code number that will be used instead of the patient's name will preserve confidentiality. No unauthorized use of this information will be allowed. Records and data that may be disclosed to any parties other than those directly involved in the treatment will not reveal the patient's identity. Under very rare and specific circumstances, the FDA and appropriate international regulatory agencies have the right to examine and copy records that identify the patient by name.

J. Conflict of Interest

None.

K. Location of the Study

The primary center for the study will be the New York Presbyterian Hospital - Columbia Campus. The clinical trial at this center will be conducted in the Interventional Cardiology Center and the Coronary Care Unit at the Milstein Hospital Building (Milstein-2S). Additionally there will be multiple sites enrolled at different institutions nationally and internationally.

L. Potential Risks

The 30-day mortality of patients presenting with cardiogenic shock ranges between 55-80%. We expect that the mortality in this study will be high.

The risks of inserting and placing a catheter in the heart include, but are not limited to: the usual risk normally associated with the administration of local anesthesia and medications required for sedation during the procedure, allergic reactions to medication or contrast dye, bleeding at the site that was used to

insert the catheter, poor wound healing, infection, the pain and discomfort of surgery, chest pain, heart or arterial wall perforation or damage from the catheters and guidewires, aneurysm, arterial spasm, irregularities in heart beat, possibly fast heart rates which may require defibrillation, or possibly too slow heart rates, requiring a temporary or permanent cardiac pacemaker, postoperative complications such as clots in the arteries of the leg or arm used for the procedure, hematoma, stroke or death.

Risks Specific To the IABP

The risks associated with IABP are:

- bleeding due to the requirement of systemic anticoagulation,
- dissection of the insertion vessel,
- device generated hemolysis; bleeding requiring transfusion;
- device engendered thromboembolic events with consequent end organ\
- dysfunction/failure-, device malfunction or failure

Risks Specific To the Use of the TandemHeart pVAD System

- creation of an atrial septal defect (ASID) as the trans-septal cannula is placed into the left atrium.
- damaging cardiac structures, or
- causing dysrhythmias during trans-septal cannula insertion or removal,
- causing an air embolism.
- dysfunction/failure;
- device malfunction or failure

M. Potential Benefits

The patient may or may not benefit personally from this study, However, information from this research may help other patients with cardiogenic shock. Both the IABP and the TandemHeart pVAD System are potentially beneficial to patients due to their potential to stabilize patients by reversing cardiogenic shock. Both treatments may also offer a bridge to a more definitive therapy after initial stabilization. The subjects will be of assistance in evaluating the efficacy of a new device used for treatment of cardiogenic shock.

N. Alternative Therapies

Alternative methods to treat cardiogenic shock include pharmacological therapy and the placement of the intra-aortic balloon pump. Approved ventricular assist devices primarily used for bridge to transplantation may be used in the short term but require surgery.

O. Compensation to Subjects

The patients will not be paid for taking part in this study.

P. Costs to subjects

For those randomized to the experimental arm, the TandemHeartTM System will be provided without any cost. The patient's participation in the study may incur additional costs that will not be covered by the hospital or by the patient's insurance company. Follow-up visits to the patient's local doctor are part of the standard clinical treatment of the patient's cardiac disease, and are the patient's responsibility.

Q. Minors as Research Subjects

Patients under 18 years of age are excluded from this study.

R. Radiation

Not applicable.

S. References

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