The efficacy of subcutaneous Enoxaparin in reducing the incidence and severity of transplant coronary artery disease in heart transplant recipients.

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A double-blind, randomized, parallel group study comparing Enoxaparin and Placebo

A. Statement of Study and Purpose Rationale

The purpose of this study is to assess the efficacy of the drug enoxaparin, a subcutaneous low molecular weight heparin, in reducing the incidence and severity of transplant coronary artery disease in heart transplant recipients. Heart transplantation is an established treatment for end-stage heart failure unresponsive to optimal medical management. With improving therapy for rejection and infection, transplant coronary artery disease (TCAD) is the major cause of death and retransplantation in cardiac transplant recipients surviving greater than one year following transplantation. Significant coronary diesease may produce arrhythmias (abnormal heart rhythms), myocardial infarction, impaired left ventricular function with congestive heart failure and sudden death. Approximately 14-35% of patients by one year and 50-91% by five years post transplantation will have angiographic evidence of TCAD and studies using intravascular ultrasound (IVUS), which is believed to be a more sensitive modality than angiography to detect TCAD, have demonstrated that 25% of patients at one year and 80% at five years show definite intimal thickening suggestive of TCAD. This suggests that TCAD appears to develop very early after transplantation and that the use of therapies thought to interfere with this process immediately post transplantation may prove beneficial in reducing the incidence and severity of TCAD.

Although the etiology of TCAD remains controversial and is likely multifactorial, endothelial (the cells lining the vessel walls) dysfunction and impaired hemostatic (clotting) function have been implicated in the development of TCAD. A recent study revealed a reduction in TCAD as well as an improved allograft survival using low molecular weight heparin (an anticoagulant, antithrombotic agent) in combination with cyclosporine in an animal cardiac transplant model. Enoxaparin, a subcutaneous low molecular weight heparin, is a fragmented form of standard heparin and is believed to have an increased antithrombotic effect when compared to unfractionated heparin. It has minimal protein binding, excellent bioavailability and a very predictable anticoagulant response. It is currently approved for use in preventing lower extremity blood clot formation in patients after hip replacement and major knee surgery. Low molecular weight heparins also possess a wide range of other effects which may be beneficial after transplantation such as the ability of heparin to favorably modulate immune function (also believed to play a role in the development of TCAD), to enhance other immunosuppressive drugs and to inhibit smooth muscle cell (SMC) migration and proliferation which has been shown to be a component of both native and transplant related arteriopathy.

B. Description of Study Design and Statistical Analysis

One hundred and twenty patients immediately after undergoing cardiac transplantation will be randomized to receive either subcutaneous enoxaparin lmg/kg twice daily (sixty patients/group) or subcutaneous placebo .01mg/kg twice daily (sixty patients/ group). Patients will be randomized in a double-blind fashion. The parallel groups will start study therapy on the day following cardiac transplantation and continue assigned treatment for thirty days.

All patients being evaluated for cardiac transplantation will be screeened after permission to approach such patients has been obtained from their attending cardiologist or cardiothoracic surgeon. The screening will be performed by the Principal Investigator of this study. Patients will then be randomized

in a double-blind fashion to receive either subcutaneous enoxaparin or subcutaneous placebo. There are no plans for crossing subjects over from one study group to another. All patients will receive standard immunosuppressive regimens including cyclosporine, prednisone and azathioprine, adjusted at the clinician's discretion.

The primary efficacy objective of this study is to demonstrate the superiority of enoxaparin lmg/kg given subcutaneously every twelve hours compared to placebo .01mg/kg also given subcutaneously every twelve hours with the primary endpoints being incidence and severity of TCAD in both groups assessed both by angiography and intravascular ultrasound at one year post-transplantation. Coronary angiograms will be performed using the Judkins technique with standard coronary angiographic views obtained. Angiograms will be reviewed by an angiographer experienced in interpreting transplant coronary angiograms who is blinded to the treatment groups. TCAD will be considered present if any one of the following four lesions previously described as evidence of TCAD is present: Type A lesion with discrete stenoses typical of native coronary artery diesease; Type B1 lesion with abrupt onset and distal diffuse concentric narrowing with eventual obliteration; Type B2 lesion with gradual onset of concentric narrowing and some residual lumen; and Type C lesion with narrowed irregular distal branches and squared off ends. In addition, angiograms will be given a grading of normal, mild, moderate or severe TCAD based on the overall appearance of the angiogram to assess severity of disease.

The primary efficacy parameter of evidence of TCAD assessed by the angiograms will be compared between treatment groups using chi-square analysis. Severity of TCAD, based on the aforementioned scale of normal, mild, moderate or severe, will be compared between treatment groups using chi-square analysis. Mortaltity from all causes will be compared between treatment groups using Kaplan-Meyer survival curves.

The expected incidence of transplant coronary artery disease which will be detected by angiograms one year post transplantation is 25% in the placebo group and based on the aforementioned animal study about 5% in the enoxaparin treatment group. Based on an 807o power to detect significance at .05, one hundred and twenty patients will be required (sixty patients per treatment group) for this study.

Intravascular ultrasound will also be performed as a secondary outcome measure of TCAD on each patient and will be reviewed by an ultrasonographer experienced in interpreting the ultrasonographic results who is blinded to the treatment groups. TCAD will be considered present if there is evidence of definite intimal thickening. TCAD as assessed by the ultrasonograms will be compared between the treatment groups using chisquare analysis.

C. Description of Study Procedures

Eligible patients awaiting cardiac transplantation will have the following pre-randomization procedures performed: explanation of the study to the patient and informed consent; medical history; complete physical examination; routine blood labs which include a CBC with platelets, PT/PTT, creatinine and liver function tests. Randomization to subcutaneous enoxaparin or subcutaneous placebo will occur immediately post transplantation. Patients meeting all the inclusion criteria and none of the exclusion criteria will be randomized to study medication (subcutaneous enoxaparin or subcutaneous placebo) in a double-blind manner. In addition to study drug therapy patients will receive standard immunosuppressive regimens including cyclosporine, prednisone and azathioprine adjusted at clinician's discretion.

Double-blind treatment will continue for 30 days post-transplantation. End of treatment is defined as the day when all subcutaneous study medication is stopped. The following will be performed starting on study day 2 and will continue throughout treatment as well as up until 1 week after the end of treatment: daily bleeding/ hemorhage assessment (major or minor); daily adverse event assessment; daily concomitant medication assessment; a CBC with platelets and liver function tests will be drawn every 5 days; a complete physical exam will be performed at the end of treatment.

All patients will undergo cardiac catherization with standard angiographic views obtained at one year post-transplantation. It should be noted that cardiac catherization. at one year post transplantation is

the standard clinical care for patients after cardiac transplantation. Patients will also undergo intravascular ultrasound at the time of this cardiac catherization.

The likely duration of the entire study is two years. Each subject's participation in the study will be for one year following transplantation.

The only additional instrumentation for this study will be the use of the intravascular ultrasound at the time of the cardiac catheterization performed one year post transplantation. Of note, intravascular ultrasound is considered the stardard of care at some hospitals and is routinely used to assess evidence of TCAD.

Patients wil not experience any additional pain, discomfort or inconvenience as a result of this study other than the fact that they will be receiving two subcutaneous injections per day for 30 days.

D. Study Drugs

Treatment with either subcutaneous enoxaparin or subcutaneous placebo will continue for thirty days following cardiac transplantation beginning on the day after transplantation and will be discontinued if the patient develops an hemorhagic stroke, thrombocytopenia (platelets less than 50,000), a severe allergic reaction, a decrease in their hematocrit requiring a blood transfusion, or dies.

In order to maintain the double-blind study design, the results of the CBC with platelets for all study patients will be made available only to an independent physician who will be unblinded to study drug treatment.

The study medication (enoxaparin and placebo) will be given subcutaneously in the anterolateral abdominal wall. For each injection, the needle will be introduced to its entire length, perpendicular to the skin fold between the thumb and the forefinger. The entire contents of the syringe will be injected into the skin fold. The skin fold will be held throughout the injection period. The site of injection will be altered each time. Patients will receive the subcutaneous injection by someone trained in giving subcutaneous injections during their post-transplant hospitalization period.

However, if the patient is discharged from the hospital prior to completing the thirty day study medication period, then either s/he or a family member will be trained in giving the injections and the remaining doses/syringes of study medication will be given to the patient on discharge from the hospital and the patient will be telephoned by the principal investigator every 12 hours to remind the patient to take the study medication.

Common side effects of enoxaparin include bruising and pain at the injection site, bleeding risk, retaining water, upset stomach, vomiting, confusion, skin rash, itchiness, fever, liver function test abnormalities, a decrease in blood platelet count, allergic reactions (chills, fever, hives), runny nose, eye tearing, asthma, a condition called "purple toes," blood vessel reactions and loss of skin tissue. Soft bones (osteoporosis) and a decrease in kidney function have been noted following long term, high dose heparin therapy. Increased blood potassium, baldness, prolonged erection, and increase in blood clots (after heparin in stopped) have also been reported. Common side effects of subcutaneous placebo injections include bruising and pain at the injection site.

E. Medical Devices

The use of intravascular ultrasound will occur at one year posttransplantation.

F. Study Questionnaires

Not applicable.

G. Description of Study Subjects and Methods of Recruitment

a. Inclusion criteria include

a. Male or female patients > 18 years old.
b. All patients who successfully undergo cardiac transplantation who do not meet any of the exclusion criteria (which are listed below). Inclusion criteria for cardiac transplantation include:
    i. Patients with end-stage cardiac disease and a life expectancy of less than one year are considered for transplantation and have one of the following:
        1. NYHA Class III or IV CHF refractory to maximal medical therapy. Objective data include a reduced left ventricular ejection fraction and a reduced functional capacity with maximal oxygen consumption < 14 ml / kg / min.
        2. Inoperable Coronary Artery Disease with intractable anginal symptoms.
        3. Malignant ventricular arrhythmias unresponsive to medical or surgical therapy.

b. Exclusion Criteria include

1) Patients who meet one of the exclusion criteria for cardiac transplantation and thus do not undergo transplantation. The Exclusion criteria for transplantation include:
    i. Age > 65 years
    ii. Severe pulmonary hypertension as evinced by a fixed pulmonary vascular resistance of greater than 6 Wood units.
    iii. Recent peptic ulcer disease.
    iv. Pulmonary infarction within the past 6-8 weeks.
    v. Evidence of end organ damage due to diabetes (e.g. retinopathy, nephropathy) and/or brittle diabetes mellitus (e.g. history of diabetic ketoacidosis).
    vi. Major chronic disabling illness (e.g. lupus, severe arthritis, neurologic diseases, residual CVA).
    vii. Symptomatic severe peripheral vascular or carotid artery disease. (Surgical intervention may permit transplant consideration on a case by case basis).
    viii. Symptomatic hypertension that requires multi-drug therapy. 1) Active infection.
    ix. Significant chronic functional impairment of other vital organs, non reversible in nature - e.g.:
        1. renal: creatinine > 2.5 or creatinine clearance < 50 ml /min
        2. liver: bilirubin > 2.5; ALT/ AST> 2X normal
        3. lungs: chronic bronchitis, chronic obstructive disease, inability to stop smoking
        4. blood: significant coagulation abnormalities, bleeding diathesis
    x. Excessive obesity (e.g. > 30% over normal).
    xi. Evidence of drug, tobacco or alcohol abuse within the past six months.
    xii. Active mental illness or psychosocial. instability.
    xiii. Active or recent malignancy.
    xiv. HIV Seroconversion.
    xv. Amyloidosis. In patients over the age of 55, the same criteria apply except the following are usually considered absolute contraindications:
    xvi. Syptomatic peripheral vascular disease or carotid disease. R) Insulin requiring diabetes. S) Evidence of obesity (> 20% above normal).
b. Allergy to pork or pork products.
c. Allergy to heparin, low molecular weight heparin or a history of heparin or low molecular weight heparin associated thrombocytopenia, with or without thrombosis.
d. Platelet count < 100,000 mm3
e. Anemia considered clinically significant - Hgb < 10.0 g/dl.
f. Current need for anticoagulation or thrombolytic therapy (e.g. pulmonary embolus or DVT.
g. Treatment with other investigational agents.

The study will not be restricted by race or gender.

H. Confidentiali1y of Study Data

All study data will be coded (without any personal identifiers) and will be stored in a secure location in the Interventional Cardiology Center at CPMC accessible only to the investigators.

A unique code number will be used for study subjects.

I. Location of Study

The study will be conducted at CPMC in clinical care areas such as the Coronary Care Unit or the Cardiology Floors (6 Hudson North, 6 Hudson South). If the patients is discharged from the hospital prior to completing the thirty day study medication period, then the study medication will be given either at the patient's home or in the Cardiology Outpatient Clinic.

J. Risks and Benefits

Bleeding is a potential risk in this protocol from the subsutaneous enoxaparin. If significant bleeding occurs, study drug will be stopped and transfusions will be given as necessary. There may be discomfort at the injection sites, bruising and/or bleeding. Blood drawing from a vein may cause bruising, localized bleeding, infection, faintness, and a small amount of pain from the puncture.

As with any drug, there is always a low risk of rare or previously unknown side effects occurring from enoxaparin.

The patient may or may not benefit personally from this study. There is no guarantee that the patient will directly benefit. Benefits may include prevention of transplant related coronary artery disease, CHF, arrhythmias or sudden death from study drug therapy. The benefit to society is that other patients who undergo cardiac transplantation may ultimately benefit in that this study may help to develop a new treatment for these diseases.

K. Altemative Therapies

none

L. Compensation and Costs to Subjects

Enoxaparin will be supplied free of costs to subjects. Compensation will not be provided for participation in this study. If during this study any injury should occur to a patient as a direct result of the administration of enoxaparin, all medical expenses necessary to treat such an injury will be paid. Patients will not incur any costs.

M. Minors and Research Subjects

Not applicable.

N. Radiation or Radioactive Substances

Cardiac angiograms incur a small amount of radiation exposure; however, patients after cardiac transplantation routinely undergo this procedure and no additional angiograms are needed for this study than the ones routinely performed for quality of care in cardiac transplant patients. Patients in this study will undergo intravascular ultrasound which will incur a small amount of additional radiation exposure. This will be explained to the patients in this study.