IRB PROTOCOL

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A Randomized, Controlled Trial Comparing Cilostazol with Extended Release Dipyridamole in the Management of Intermittent Claudication in Peripheral Artery Disease

A. Study Purpose:

The main goal of this prospective, double-blinded, randomized, controlled, trial is to compare the efficacy of extended-release dipyridamole with cilostazol in the management of lower extremity claudication in patients with peripheral vascular disease (PAD).

B. Rationale:

Intermittent claudication (IC) is defined as a reproducible discomfort of a defined group of muscles which is induced by exercise and relieved with rest. The symptoms result from an imbalance between supply and demand of blood flow that fails to satisfy ongoing metabolic requirements. [1] Not only is PAD now considered coronary heart disease (CHD) equivalent, symptomatic PAD contributes significantly to the morbidity and quality of life in patients with IC. The prevalence of IC would appear to increase from about 3% in patients aged 40 to 6% in patients aged 60 years. [2] Despite this prevalence, the treatment options for IC are limited. The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II (TASC II), a working group of expert representatives recently published a summary of all the evidence for the particular drug therapies available for the management of IC in the United States being limited to cilostazol, a phosphodiesterase III inhibitor with vasodilator, metabolic and antiplatelet activity. Though many other drugs have been studied including other vasoactive and antiplatelet agents, only one other drug, naftidrofuryl (l5-hydroxytryptamine type 2 antagonist), a drug available only in Europe has shown comparable efficacy in the management of IC. However, older, smaller studies done on the combination of ASA-dipyridamole have shown some efficacy in the management of IC. One showed that symptoms-free walking time on the treadmill was improved with the combination of anti-platelet therapy. [3]A few articles in the literature of PAD elute to the use of ASA-dipyridamole in the management IC. Though this is another possible avenue for the management of IC the combination has never been studied in comparison to cilostazol. Furthermore, extended release dipyridamole(ER-DP) and aspirin (ASA) combination therapy is now being used in the secondary prevention of ischemic stroke as it has shown to cause a significant reduction in recurrent stroke and possibly decrease the overall mortality. [4, 5]Given these results, there may be an added importance of doing this study given that patients with PAD may also have an increased prevalence of cerebral vascular disease. [6]

C. Methods

a) Conceptual and Operational Definitions

The primary outcome that will be assessed in the study is maximal walking distance (MWD). Other endpoints that will be studied will include pain-free walking distance (PFWD) and change in the ankle-brachial index (ABI) at baseline, 8 weeks and 16 weeks. The secondary outcomes that will be measured are number of patients that transition from

medical to surgical intervention, number of change in medical therapy, and event rate of bleeding complications. Functional status measures of each subject will be evaluated using including the Medical Outcomes Scale (SF-36) and Walking Impairment Questionnaire at baseline, 8 weeks and 16 weeks to assess the subject's perceived improvement or deterioration of symptoms. If satisfactory results are obtained, then this study data can be used to pilot a study of adequate power to evaluate if the ER-DP arm has any effect on cardiovascular mortality including myocardial infarction (MI) and ischemic stroke.

PFWD is defined as the distance walked on a treadmill (standard, non-inclined, steady rate to be determined) from Time 0 minutes to time at which to subject first experiences claudication. MWD is defined as the distance walked on the treadmill from Time 0 minutes to the maximum distance tolerated after the onset of claudication. ABI will be measured using duplex ultrasonography at rest and after MWD at each time point. Each measurement will be repeated on three separate days and the mean of the measurements will be used in final calculations.

b) Study Design

A prospective, double-blinded, randomized, controlled design will be used to carry out the study. There will be two major arms of the study. This will be an interventional study with the first arm containing patients with ASA/cilostazol and the second arm will be subjects that were treated with ASA/ED-DP. Summary of each of the time points is as below:

Initial Screening: 1500 subjects with symptomatic claudication will be the presence of PAD will be verified using ABI and treadmill testing. An ABI of 0.90 or lower after 10 minutes of rest and by a reduction in the blood pressure of at least one ankle artery by a minimum of 10 mm Hg when measured 1 minute after claudication-limiting treadmill testing. If these criteria were not met, a decrease of at least one ankle artery blood pressure by a minimum of 20 mm Hg when measured 1 minute after treadmill testing was accepted for entry into the study. Of these selected subjects 1230 will then be randomized into two groups for further testing. [7]

Baseline: Medical Outcomes Scale (SF-36) and Walking Impairment Questionnaire (WIQ), ABI measurement at rest, treadmill testing for PFWD and MWD. Post-MWD ABI will then be measured. The treadmill testing will be repeated two additional times on two separate occasions. The average of the three PFWD and MWD will be used in final calculations.

8 and 16 Weeks Follow-Up: again SF-36 and WIQ will be administered and the protocol will be followed as above.

c) Statistical Analysis and Sample Size

The primary variable that will be analyzed is analyzed is MWD as measured by standardized treadmill testing. Additional efficacy outcomes measured will include PFWD, ABI, percent of patients needing surgical intervention or change in medical therapy in each group, and the functional status questionnaires. Based on previous study using cilostazol by Money et al., [7] using an unpaired-t test, the sample size necessary to show a statistical difference with a $p<0.05$ and a power 80% will be 615 patients in each group. The baseline comparability between the treatment group and the placebo groups will be assessed by comparing means, standard deviations, and proportions. In addition, results will be expressed as change from baseline in meters and as change in seconds walked. Estimated treatment effects will be calculated with a ratio of the geometric means (ASA-ER-DP/ ASA-cilostazol) to provide an estimate of the net drug effect. Subjective improvement of claudication, as will be assessed by the patient will be analyzed using the Cochran-Mantel-Haenszel test. The results of the study will be adjusted for age, sex, smoking history, total cholesterol, LDL levels, diabetes and other variables that may affect PAD.

D. Subject Selection

Subjects above the age of 40 years with claudication symptoms will be screened for definitive diagnosis of PAD using an ABI of less than 0.9 or if they meet the treadmill criteria noted above.

Exclusion criteria for the study would be as follows:
1) Limb-threatening PAD, including gangrene or ischemic rest pain
2) Prior surgical or endovascular procedures to treat PAD
3) Gross obesity
4) Hypertension, >200 systolic or >100 diastolic (mm Hg)
5) Current malignancy (except basal cell carcinoma or in situ carcinoma)
6) Buerger's disease or deep venous thrombosis in the previous 3 months
7) Inability to complete treadmill testing for reasons unrelated to IC
8) Bleeding problems
9) Drugs with significant effects on peripheral vessels, bleeding, hemostasis, or platelet function are prohibited during the study including warfarin, heparin, and pentoxifylline. Antiplatelet agents, such clopidogrel, ticlopidine, and non-steroidal anti-inflammatory agents are also prohibited.
10) Known or documented allergy to any of the study drugs

E. Study Drugs

The two drug combinations used in the study will be ASA/cilostazol and ASA/ER-DP. Both cilostazol and ER-DP are phosphodiesterase inhibitors with antiplatelet and vasodilatory properties that make them suitable for the study. Extended release dipyridamole will be used instead of its immediate release formulation.
Cilostazol will be dosed at 100mg twice a day, ER-DP at 200mg twice a day and ASA at 81mg once a day.

F. Study Questionnaires

The SF-36 is a general health questionnaire that measures the patient's perception of physical health, mental health, and combined physical and mental health. Four parameters (physical function, bodily pain, role-physical, and general health perception) compose the physical component scale. The WIQ assesses the patients' impressions of walking speed and distance and specific measures of walking difficulty because of pain or other problems.

G. Confidentiality of Study Data

Subject confidentiality will be maintained throughout the study by using a unique code to identify each subject. The code will only be accessible to investigators of the study. All data collected will be stored in a safe area that is accessible to the study investigators alone.

H. Location of the Study

Subjects for this study will be enrolled from the patient population at New York Presbyterian Hospital-Columbia University Medical Center out-patient Vascular Surgery and Cardiovascular Medicine clinics.

I. Risks and Benefits

The potential risks to the subjects of the trial would be side effects and bleeding complications from the drugs used in the study. On each visit the subject’s vital signs and electrocardiogram will be done and their medication changes will be reviewed to ensure their safety. The potential benefits of this study would be to find a new alternative in the medical therapy of claudication.

J. Alternative Therapies

Surgical intervention for claudication that will not respond to medical management and significantly impairs the subject’s quality of life, critical limb ischemia, gangrene, and non-healing ulcers in PAD.

K. Compensation and Costs to Subject

The study will be at no cost to subjects. However, they will be compensated for travel and time. In addition, a small amount will be added as incentive to participate in the study. Drugs used in the study will be provided by the investigators of the study via the Research Pharmacy to ensure blinding and randomization.

L. Minors as Research Subjects

None

M. Radiation or Radioactive Substances

None

N. References:

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