Phosphodiesterase Type 5 Inhibition to Improve Endothelial Function and Vascular Remodeling in Chronic Kidney Disease and End Stage Renal Disease Patients Requiring New Arteriovenous Fistula

Study Protocol and Statistical Analysis Plan

NCT Number: NCT02414204

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Protocol

1. Background:

The vascular access is the "Achilles Heel" of the hemodialysis procedure. 60% of arteriovenous fistulas (AVFs) created fail to mature adequately for hemodialysis (AVF non-maturation), due to a combination of early aggressive venous neointimal hyperplasia development and inadequate vasodilation (adverse remodeling). At present, there are no effective therapies to treat vascular access dysfunction. The treatment paradigms to date have focused on delivery of therapies post-AVF creation and most recently at the time of surgery. Preliminary data from the Hemodialysis Fistula Maturation (HFM) consortium suggests that profound endothelial dysfunction, as measured by flow-mediated (FMD) and nitroglycerin-mediated (NMD) in the brachial artery, is present in the large majority of patients prior to AVF creation. This suggests that the vascular health of the vessels at the time of AVF creation may play an important role in AVF non-maturation. Furthermore, the period immediately after AVF creation is important because the blood vessels are adjusting to new hemodynamic parameters. There are no previously published studies addressing therapies to modify or improve endothelial function prior to and after vascular access creation. Sildenafil, a phosphodiesterase 5 inhibitor that enhances the effects of nitric oxide (NO), has been shown in experimental and clinical studies in cardiovascular disease to improve endothelial function and decrease vascular stenosis. Therapies to enhance endothelial function, through NO production, have not been evaluated in vascular access dysfunction to date and may be beneficial in AVF maturation.

2. Recruitment Population:

Patients with stage IV and V chronic kidney disease and end stage renal disease requiring hemodialysis at UAB Dialysis Clinics will be recruited from the UAB Vascular Access Clinic, which has been the site for recruitment of patients requiring new vascular access for the last 10 years.

3. Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Age ≥19 years of age male or female
2. Chronic Kidney Disease Stage IV or V patients or End Stage Renal Disease Patient requiring arteriovenous fistula surgery

Exclusion Criteria:

1. Patient currently on nitrate therapy or any nitric oxide donor in any form
2. Patient currently on protease inhibitor or non-nucleoside reverse transcriptase inhibitor
3. Patient with resting systolic blood pressure <90 mm Hg and diastolic blood pressure < 50 mm Hg.
4. Patient life expectancy < nine months.
5. Patient unable or unwilling to meet study requirements.

4. Randomization Process:

Sidenafil will be purchased and obtained by the UAB pharmacy. The pharmacy will over-encapsulate the Sildenafil tablets to match a placebo encapsulated tablet.

The first subject recruited will be unblinded and receive Sildenafil. After the first subject, all subsequent subjects will begin the randomization process.

Randomization Process: Subjects agreeing to this study will be randomized at the 1st vascular function testing visit. 20 numbers generated by a biostatistician will be randomly assigned numbers to the Sildenafil treatment group (10 numbers) and randomly assigned to the placebo (10 numbers). The investigators and clinical coordinators will be unblinded to the treatment group of the subject and have access to the randomization assignments.

1. Treatment/Intervention Group: 10 patients will take Sildenafil 20 mg twice a day oral from the time after randomization (1st vascular test visit) until the 2 weeks post-operative arteriovenous fistula ultrasound.

2. Placebo Group: 10 patients will take placebo twice a day oral from the time after randomization (1st vascular test visit) until the 2 weeks post-operative arteriovenous fistula ultrasound.

5. Procedures and Study Visits:

Study Procedures:

Randomization will occur at the time of the 1st vascular function testing. The first subject will be unrandomized and receive Sildenafil. Subsequent subjects will be randomized to receive either

Sildenafil 20mg twice a day or placebo twice a day, based on randomization scheme. Subjects will begin either placebo or Sildenafil after randomization during the first vascular function visit until the 2 weeks postoperative arteriovenous fistula ultrasound.

Enrolled subjects will have an initial brachial artery flow-mediated dilation (FMD) and venous plethysmography (VP) studies performed approximately 2 weeks prior to scheduled AVF creation and a subsequent FMD and VP study prior to surgery. The FMD and VP studies are non-invasive studies. Completion of these studies will take approximately 3-4 hours.

Up to four teaspoons of blood will be drawn at the 1st FMD/VP study prior and second FMD/VP study. Blood samples will be obtained using the standard method used to obtain blood for routine hospital tests. Completion of blood draw will take approximately 10-15 minutes.

Pre-operative, 2 weeks and 6 weeks post-operative ultrasounds will be performed on participants. The pre-operative and 6 week ultrasounds are part of standard medical care and will be performed whether the participant is in the study or not.

Discarded vein and artery specimens (approximately 5-10 mm each) will be collected at the time of AVF surgery. This procedure requires 3-5 minutes, and does not affect surgical outcome.

A total of 21 subjects will be recruited for this study with prospective follow-up. The first patient will be unblinded and receive the drug. Subsequently, 10 subjects will be randomized to receive 20 mg of Sildenafil twice a day oral and 10 patients randomized to receive placebo twice a day oral. Information related to demographics, comorbidities, and AVF outcome following surgery will be collected. The primary clinical endpoint is change in baseline and 2 week FMD/VP measurements. The secondary outcome is change in blood flow and vein and artery diameters at 2 and 6 weeks.

Study Visits:

Visit 1: Screening and enrollment 1-2 hours (Research)

- Informed consent
- The study team will determine qualification to participate in this study

Visit 2: Baseline Visit (in some cases Visit 1 and 2 could be combined) (Research)

- Detailed medical history
- Height and weight measured
- Blood draw (in some cases this could occur in the dialysis unit)

Visit 3: 1st Vascular Function Test and Pre-operative Ultrasound

- Vascular Ultrasound (Standard care)
- Vascular Function Testing (3-4 hours)
    - Brachial artery flow mediated vasodilation and venous plethysmography (Research)
- Blood draw (if not collected during visit 2) (Research)
- Randomization to either study drug Sildenafil or placebo

Visit 4: 2nd Vascular Function Test

- Vascular Function Testing (3-4 hours)
  - Brachial artery flow mediated vasodilation and venous plethysmography (Research)

Visit 5: Arteriovenous Fistula Surgery

- Fistula creation (Standard care)
- Discarded vein and artery tissue collection (Research)

Visit 6: 2 Weeks Post-Operative Ultrasound

- Vascular Ultrasound (Research)

Procedures and Length of Time:

Procedure	**Length of Time Required of Participants**	**Frequency of Repetition**	**Research (Res) – OR- Routine Care**
Blood Drawing	10-15 minutes	Baseline Visit Week 2	☒Res ☐ Routine ☒Res ☐ Routine
Height and Weight	5 minutes	Baseline visit	☒Res ☐ Routine
Taking Sildenafil 20 mg or Placebo bid oral	2 minutes	Daily from the time after randomization (1st vascular test visit) until the 2 weeks post-operative arteriovenous fistula ultrasound	☒Res ☐ Routine
Vascular Function Testing –FMD and VP	3-4hrs	Pre-operatively at baseline Two weeks after baseline	☒Res ☐ Routine ☒Res ☐ Routine
Vascular Ultrasound	1-2hrs	Pre-operative Week 2 Visit Week 6 Visit	☐Res ☒ Routine ☒Res ☐ Routine ☐Res ☒ Routine

Discarded Vein and Artery Tissue Collection	3-5 minutes of surgery time	Once	☒Res ☐ Routine

6. Length of Time of Follow-up and Subject Participation:

Total Follow-up Time: 2 years to follow clinical data related to clinical survival of the fistula.

Total Participant Time: Up until the six week postoperative ultrasound.

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Statistical Analysis Plan

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The data will be analyzed in two stages: (1) descriptive statistics, which will include means and standard deviations for normally distributed continuous variables, medians and interquartile ranges for skewed continuous variables, and proportions for categorical measures and (2) two-group t test, Wilcoxon rank-sum tests, chi-square tests, and simple logistic regression and multiple logistic regression modeling. P values <0.05 will be considered statistically significant.