Official Title: Bovine Carotid Artery Biologic Graft and Expanded Polytetrafluoroethylene for Permanent Hemodialysis Access

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JHM IRB - eForm A – Protocol

A Prospective Randomized Study of Bovine Carotid Artery Biologic Graft and Expanded Polytetrafluoroethylene for Permanent Hemodialysis Access

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Type of Study: Investigator initiated study. The principal investigator will have sole responsibility for monitoring and oversight of problem/events for this research.

Institution: Johns Hopkins Medical Institutions, Baltimore, MD, USA

1. Abstract

Arteriovenous grafts (AVG) remain reliable substitutes for permanent hemodialysis access in scenarios that preclude the placement of arteriovenous fistulae. There is scarcity of evidence to support the current preference of synthetic conduits over biologic grafts in clinical practice. Advances in the design of AVG's warrant contemporary comparisons between synthetic and biologic AVG options. This is especially important as biologic conduits may confer an advantage by virtue of their inherent similarity to the native human vasculature. We propose a randomized study to compare bovine carotid artery (BCA) biologic grafts and expanded polytetrafluoroethylene grafts (ePTFE) for permanent hemodialysis access.

2. Objectives

The overall goal of this project is to compare the one and two year patency, complication and intervention rates between BCA and standard ePTFE.

Specific Aim 1: To compare functional primary patency between BCA and ePTFE

Hypothesis 1A: Patients receiving BCA grafts will have a higher primary patency rate at 1 and 2 years follow up than those who receive ePTFE grafts.

Specific Aim 2: To compare functional primary assisted patency between BCA and ePTFE

Hypothesis 2A: Patients receiving BCA grafts will have a higher functional primary assisted patency rate at 1 and 2 years follow up than those who receive ePTFE grafts.

Specific Aim 3: To compare functional secondary patency between BCA and ePTFE

Hypothesis 3A: Patients receiving BCA grafts will have a higher functional secondary patency rate at 1 and 2 years follow up than those who receive ePTFE grafts.

Specific Aim 4: To compare complication (pseudoaneurysms, infection and steal syndromes) rates between BCA and ePTFE

Hypothesis 4A: Patients receiving BCA grafts will have lower complication rates at 1 and 2 years follow up than those who receive ePTFE grafts.

Specific Aim 5: To compare re-intervention rates between BCA and ePTFE

Hypothesis 5A: Patients receiving BCA grafts will have a lower re-intervention rate at 1 and 2 years follow up than those who receive ePTFE grafts.

Primary outcomes: Primary, primary assisted and secondary patency rates at 1 and 2 years.
Secondary outcomes: Complication (pseudoaneurysms, infections and steal syndrome) and re-intervention rates at 1 and 2 years.

3. Background

It is known that arteriovenous fistulae (AVF) confer a clear benefit for hemodialysis access in patients with end stage renal disease (ESRD). As a result, national guidelines stipulate AVF as the preferred mode of permanent hemodialysis access[1]. In practice, not all patients are good candidates for AVF due to unavailable or inadequate venous conduit(s). In these patients, arteriovenous grafts (AVG) serve as reliable substitutes.

Synthetic grafts such as those made from expanded polytetrafluoroethylene (ePTFE) are the most common AVG's in current use. However, significant drawbacks of ePTFE have been reported in relation to long term patency and infection rates[2-4]. These inadequacies inform the need to develop and evaluate biologic conduits that achieve closer mimicry of native human vessels and as result may overcome the disadvantages associated with synthetic grafts.

Since the use of bovine carotid artery (BCA) biological grafts began in the 1970's[5-8], significant advances have been made in conduit design and techniques for AVG placement and postoperative endovascular

management. Despite the wide spread use of ePTFE, there is lack of current evidence of a clear advantage of ePTFE over biologic conduits. Prior comparative studies were based on patient cohorts drawn from prior decades[9,10,11]. This questions the bases for the preference of synthetic conduits in this age. In addition to this lack of current evidence, the more recent study was based on a small cohort of patients[10]. Consequently, these inadequately powered studies were unable to establish superiority between AVG options.

There are over 400,000 patients in the United States who are currently on hemodialysis. An estimated 110,000 new patient annually develop ESRD, requiring dialysis or kidney transplant[12]. A conduit that confers better outcomes based on objective evidence will significantly impact the economy and patients' quality of life. In order to address the aforementioned knowledge gaps, we propose a prospective randomized study comparing the functional long-term outcomes between biologic and synthetic AVG conduits in a large cohort of patients. The results of this study will generate evidence needed to inform choice of AVG for permanent hemodialysis access.

4. Study Procedures

a. Study design.

Prospective Randomized Clinical Trial.

Screening

Candidates will be screened for eligibility for the study when evaluated for graft placement as per standard of care. The screening will take place in inpatient or outpatient clinic at either Johns Hopkins Bayview Medical Center or Johns Hopkins Hospital. Physical exam and preoperative vein mapping, if necessary, will be obtained to ensure the unavailability of an autogenous alternative. These surgeries will be elective in nature. Women of child bearing age will be given a urine pregnancy test preoperatively as per standard of care. Those who are pregnant or plan on becoming pregnant for the duration of the study are excluded. Candidates who meet the general inclusion / exclusion criteria will be approached for consent. All HIPAA patient privacy regulations will be observed during discussions with patients.

Consent

Patients will be recruited by the surgery services at Bayview Medical Center or Johns Hopkins Hospital. Patient history and routine preoperative tests will be used to identify comorbidities (such as diabetes, immunosuppression and smoking). Hopkins IRB approved consent designee for this study will meet with the patients prior to the operation to discuss the purpose of the trial and the subject's role, should they choose to participate. The patient will be informed in detail about the study and all their questions will be answered before signing the consent form. The patient will be given ample time to consider the study and

will also be given a chance to review the informed consent form (ICF). They will have the option of taking the ICF home or having it mailed or emailed to them before making any decisions. No study related procedures would be performed before written informed consent process. All HIPAA privacy regulation applies here and patient rights as well as responsibilities are incorporated in the informed consent process. Consenting patients will be enrolled into the study and prospectively randomized to receive either BCA or standard ePTFE by an independent study coordinator.

Enrollment

Once enrolled, patients will be randomized to one of two groups: one group will receive the BCA graft (experimental) while the other group will receive any standard ePTFE graft (control). Randomization will be done via a computer-generated list of numbers in a 1:1 ratio using the online tool Research Randomizer.

AVG Placement

Patients will undergo surgery as per standard of care and receive the randomized graft in compliance to National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for AVG creation[1]. The grafts will be placed either in the arm (brachial artery-axillary vein) or forearm (brachial artery to cephalic or suitably sized vein) based on anatomic suitability.

Post-Operative Assessment

The patients and their grafts in both treatment arms will be monitored postoperatively per standard stipulated by KDOQI. In the immediate post-operative period, particular attention will be paid to the presence of thrills or bruits within the graft by the examiner(s) as well as neurologic and circulatory function of the ipsilateral hand. At hemodialysis the grafts will be accessed with 15 or 17 gauge needles inserted at any angle between 25-30 degrees (the same method used for a native arterio-venous fistula).

b. Study duration and number of study visits required of research participants.

Follow-up

1) POD# 10-20: Physical examination by the surgeon or PA as per standard of care. Any thrills or bruits as well as any neurological or circulatory abnormalities in function of the ipsilateral hand will be noted by the examiner.

2) POD# 25-45: Physical examination by the surgeon or PA as per standard of care. Any thrills or bruits as well as any neurological or circulatory abnormalities in function of the ipsilateral hand will be noted by the examiner.
3) Thereafter; dialysis center 3 times weekly: The graft will be monitored for its functionality during dialysis sessions three times weekly by the nephrologists or trained dialysis nurses. Difficulty during dialysis (disruptions in flow pattern or increased bleeding) or the absence of a thrill or bruit will warrant surgical evaluation. If by physical examination the graft is thrombosed, then the patient will immediately be referred for endovascular thrombectomy and revision. If the graft is patent, but problematic, the patient will be referred for an urgent fistulogram and endovascular intervention.

Patients, dialysis and dialysis access centers will be contacted by the fellow or study coordinator **every three months up to two years** to ascertain function of the graft and monitor outcomes of interest.

Note: This time frame for follow up was chosen because:

a) It will minimize data lost to follow up.
b) It will maximize the opportunity for detection of infection, malformations or stenoses since most graft abnormalities are apparent by 30 days postoperatively.
c) The standard of care at the Johns Hopkins surgical department includes a post-op check and visit 5 to 14 days following surgery.
d) The follow up continues up to 2 years to report the final outcomes at end of the study.

Outcomes

Outcomes will be assessed and documented per standards for reports dealing with arteriovenous hemodialysis access[13] and defined as follows. Primary patency: Interval from graft placement to any intervention for stenosis with or without complete occlusion (thrombosis). Assisted primary patency: interval from graft placement to the first episode of complete occlusion. Secondary patency: interval from graft placement to graft failure. Functional patency: interval from first time graft is used for hemodialysis to qualifying event as above. Infection will be defined as the presence of erythema or purulent drainage at

the surgical incision and need for intravenous antibiotics or surgical intervention. Steal syndrome will be staged per standard as follows: Stage I: pale/blue and/or cold hand without pain; Stage II: Pain during exercise and/or hemodialysis; Stage III: Rest pain; Stage IV: Ulcers/necrosis/gangrene. Accordingly, surgical intervention will be carried out for patients with stage III or IV steal.

Innovation

This study addresses the need for an objective comparison of contemporary AVG options available to patients and their surgeons. The key innovative aspects of this study are:

1. Randomization of patients to minimize the effects of measured and unmeasured confounders.
2. Study of a present-day cohort of patients so as to derive evidence applicable to contemporary practice.
3. Study of a sample of patients large enough to achieve statistical and clinically significant results.

In this study we will conduct a randomized comparison of bovine carotid artery biological grafts (Artegraft®; Artegraft, Inc., North Brunswick, NJ) to standard polytetrafluoroethylene grafts. Our goal is to establish differences in patency (functional, primary, primary assisted and secondary), complication and intervention rates.

Problems and solutions

Despite our conservative estimate, we are prepared for the possibility of inadequate enrollment in this study. In the event that we are unable to achieve a sample of patients required for well-powered analyses, we will extend patient recruitment to other hospitals on the Johns Hopkins Medical Institution network. This large back up pool of patients is reassuring.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

This study will not be blinded because patient side blinding is expected to have minimal to no effect, while physician side blinding is impractical and difficult to achieve due to the primary surgeon being the one usually who follows up on any future interventions or treatments.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

All participants will receive routine care and will not have current therapy stopped.

e. Justification for inclusion of a placebo or non-treatment group. **Not applicable**

f. Definition of treatment failure or participant removal criteria.

In case of intolerance or development of an allergic reaction (such as severe incision site skin irritation or discomfort) the PI or co-PI will decide whether to remove the graft or replace it and the patient's hypersensitive reaction will be treated according to best medical practice.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely. **Not applicable**

5. Inclusion/Exclusion Criteria

Inclusion criteria

1. Patient must be at least 18 years of age.
2. Patient has been informed of the nature of the study, and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB) / Medical Ethics Committee (MEC) of the respective clinical site.
3. Patient meets the criteria for and is undergoing Arterio-Venous-Graft surgery at Johns Hopkins Medical Institutes.
4. Patient agrees to return for all required clinical follow up for the study.

Exclusion criteria

1. Known allergic reaction or history of intolerance to any ePTFE or BCA components.
2. Local infection at AVG placement site at the time of surgery.
3. Bleeding disorder or refuses blood transfusion.
4. Presence of active malignancy and/or life expectance is less than 1 year.
5. Patient is pregnant or plans to get pregnant for the duration of the study.
6. Any patient who is eligible to receive an Arterio-Venous-Fistula.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.
Eligible vascular patient candidates who will receive the BCA graft will have improved primary, primary assisted and secondary patency as well as lower complication and re-intervention rates compared to the standard ePTFE graft.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. **Not applicable**

c. Justification and safety information if non-FDA approved drugs without an IND will be administered. **Not applicable**

7. Study Statistics

a. Primary outcome variable.

Primary patency, primary assisted patency and secondary patency at 1 and 2 years.

b. Secondary outcome variables.

   Complications and re-intervention rates at 1 and 2 years.

c. Statistical plan including sample size justification and interim data analysis.

All data will be stored in a secure database housed by the Vascular and Endovascular Clinical Research Center at Johns Hopkins Bayview Medical Center. Data cleaning and resolution of queries will be carried out continuously through the study period. Univariate methods (Chi Square, ANOVA, t-test) will be employed to compare patients' characteristics. Kaplan Meier and Multivariate Cox proportional regression analyses will be employed to evaluate and compare outcomes between BCA and ePTFE over time. Interim statistically analysis every 6 months between the cohorts will be performed to ensure unbiased distribution of possible confounders. If a bias is found (uneven comorbid conditions distribution), an effort will be made to correct it. All analyses will be performed using Stata version 12.1 (Statacorp, College Station, Texas). P-values less than 0.05 will be accepted as significant.

Sample Size

Specific Aims 1-3

Based on data from a prior study[10] primary assisted patency of BCA was 60.5% and 40.5% at 1 and 2 years respectively. Primary assisted patency of ePTFE was 20.8 and 13.8% at 1 and 2 years, respectively. Based on an 80% power and an alpha of 0.05, the minimum sample size required to detect a 30% difference in assisted patency in a two-tailed comparison of BCA vs. ePTFE is 49 patients per group (for a total of 98 patients).

Specific Aim 4

Based on data from a prior study[10], complication rates were 0.77 in ePTFE and 0.34 in BCA. Based on an 80% power and an alpha of 0.05, the minimum sample size required to detect a 30% difference in complications in a two-tailed comparison of BCA vs. ePTFE is 47 patients per group (for a total of 94 patients).

Specific Aim 5

Based on data from a prior study[10], the total number of intervention for BCA was 1.45 ± 0.19 and 1.99 ± 0.25 for ePTFE[6]. Based on an 80% power and an alpha of 0.05, the minimum sample size required to detect a 20% difference in intervention rates in a two-tailed comparison of BCA vs. ePTFE is 47 patients per

group (for a total of 94 patients).

Based on these estimates, this study will be conducted on a minimum sample of 100 patients with 50 patients in each treatment arm.

d. Early stopping rules.
   1. Inability to tolerate BCA graft
   2. Allergic reaction to the BCA graft
   3. Statistical evidence that the BCA has better outcomes versus the standard ePTFE*

*we will carry out a review of the outcomes every 6 months in this study

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency. Generally speaking there is minimal risk in participating in this study. If the patient is randomized to the standard ePTFE, they will receive our hospital's standard of care for ePTFE AVG. If the patient is randomized to the BCA graft they may experience the following:

1. Discomfort and inability to tolerate the BCA graft: In this situation the graft will be inspected by the Principle Investigator, co-PI or wound nursing team. In the event that the patient is still unable to tolerate the graft, it will be removed or replaced and the patient will be excluded from the study.

2. Skin abrasion or irritation: If on inspection the skin edges at the incision site appear to be red or irritated the PI, co-PI or wound nursing team will inspect the site of operation and determine whether the graft needs revision or removal.

3. Allergic reaction to the device: Since BCA is an acellular collagen matrix, it is tested as non-antigenic and packaged sterile in its container. However, any foreign material may cause a reaction. If at any time during the study the patient appears to have an allergic reaction to the BCA. The Principle Investigator or co-PI will determine if the graft needs to be removed and the patient will be removed from the study.

4. Redness or erythema, fever, signs of infection: Should there be any concern for infection of the graft, the surgery site will be assessed by the Principle Investigator, co-PI, Nurse Practitioner or Physician Assistant. Appropriate standard of care will be initiated should the wound indeed be infected. This may include opening and draining the incision, wet to dry dressing changes and antibiotics treatment.

b. Steps taken to minimize the risks.

Follow standard surgical procedures and placement of AVG.

c. Plan for reporting unanticipated problems or study deviations.

All events will be reported to the JHM IRB as required by the JHM IRB reporting guidelines posted on the JHM IRB website.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

There should be no legal risks by participating in this study. None beyond those associated with routine care.

e. Financial risks to the participants.

None beyond those associated with routine care.

9. Benefits

a. Description of the probable benefits for the participant and for society.

No direct benefits for study subjects, but the results of this work may improve care of future vascular patients.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

There is no compensation to participate in this study. We are randomizing patients to standard ePTFE graft versus BCA graft. There are no extra visits or extra time involved above and beyond the standard of care for the patient.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

Costs of the BCA graft and ePTFE grafts are being covered by insurance or participants themselves because both are standard of care. Participants or insurance are responsible for paying the cost of the routine standard of care and follow-up clinical examination visits, which are the standard of care, that are included following surgery.

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