TITLE:
Randomized Comparative Evaluation of Midline Catheters for Thrombophlebitis

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Protocol and Statistical Analysis Plan

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Introduction

Establishment and maintenance of intravenous (IV) access are core processes in providing medical care for hospitalized patients. For patients requiring extended duration of therapy, the peripherally inserted central catheter (PICC) Team is often consulted for patient assessment and vascular access device placement at many hospitals. PICCs are central catheters that are placed via peripheral vein under ultrasound guidance and may be used for patients with difficult venous access for long-term central or peripheral infusion therapies as well as central venous pressure monitoring in a critical care setting. Although PICCs provide a great option for some patients, these catheters have known complications including catheter- related bloodstream infection, catheter-related venous thrombosis, malfunction, and high cost. Midline catheters represent a potentially attractive alternative to PICCs for peripheral infusions. These catheters have been utilized since the mid 1980s but fell out of favor in the early 1990s due to reports of acute life threatening hypersensitivity reactions. In the last few years, midlines have made a resurgence in the market and are FDA cleared for use in patients requiring intermediate to long-term infusion therapies. Advances in midline catheters offer the potential for reduced complications. As midlines have increased in popularity and new midlines have been introduced into the market, it is necessary to better understand complication profiles of various midline catheters, as it is likely that all catheters are not created equal. Specifically, the incidence of symptomatic catheter-related thrombosis is of interest. While this complication has been researched extensively for PICCs with an incidence of 1.8 – 8.4%, data on this complication for midlines represents a gap in the literature. One recent publication cited a 4.5% rate of all symptomatic catheter-related venous thrombosis (combined superficial venous thrombosis (SVT) and deep venous thrombosis (DVT)) in patients with midline catheters. Another study found a catheter-related venous thrombosis rate of 2.5% when limiting measured outcomes to occurrence of DVT . Internal retrospective data at our institution suggests a rate closer to 12-15% for all symptomatic catheter-related venous thrombosis (SVT and DVT). Some midline catheters are coated to provide protection against catheter-related venous thrombosis and/or catheter-related bloodstream infection. The theoretical benefit(s) of these catheters need further validation in human subjects.

Objective

We aim to understand the difference in symptomatic catheter-related upper extremity venous thrombosis (CR-UEVT) comparing the Teleflex Arrowg+ard Blue Advance 4.5 F single lumen midline catheter to the AngioDynamics BioFlo 4 F single lumen midline catheter. Both catheters are inserted using a modified seldinger technique (MST). The AngioDynamics product has Endexo technology with claims of reduced platelet aggregation and favorable thrombus accumulation profile. The Teleflex catheter is a chlorhexidine coated device that claims to be both antithrombogenic and antimicrobial.

Specific Aim 1: To compare incidence of symptomatic CR-UEVT between the AngioDynamics Bioflo midline catheter and the Teleflex Arrowg+ard Blue Advance midline catheter.

For Aim 1, we will measure incidence of all symptomatic CR-UEVT inclusive of superficial thrombophlebitis (SVT) and deep venous thrombosis (DVT) confirmed by upper extremity venous doppler evaluation, to assess whether Arrowg+ard midline catheters offer a reduction in the incidence of symptomatic CR-UEVT.

Specific Aim 2: To compare incidence of catheter-related bloodstream infection between the AngioDynamics BioFlo midline catheter to the Teleflex Arrowg+ard Blue Advance midline catheter.

For Aim 2, we will identify cases of infection per the laboratory confirmed bloodstream infection criteria published by the Center for Disease Control (CDC), to assess whether Arrowg+ard Blue Advanced midline catheters offer reduction in catheter-related bloodstream infection.

Alternatively, for Aim 1 and Aim 2, to further examine the incidence of overall complications in the light of the differing catheter dwell times, catheter days data (including multiple insertions of midline catheters per patient in the study period) will be analyzed.

Specific Aim 3: To compare catheter survival rate data between the AngioDynamics BioFlo midline catheter and the Teleflex Arrowg+ard Blue Advance midline catheter.

For Aim 3, an improved survival of Arrowg+ard Blue Advanced midline catheters will be evaluated by functionality of catheter for intravenous therapy prior to patient discharge. The event is failure of functionality identified during follow-up assessment during hospitalization. Duration of dwell and functional failure of the catheter will be employed to estimate catheter survival.

Study Design

We propose a prospective single-site, parallel, two-arm, randomized investigation to assess catheter-related symptomatic UEVT, catheter-related bloodstream infection, and functionality of two single lumen midline catheters: AngioDynamics BioFlo 4 F and Teleflex Arrowg+ard Blue Advance 4.5 F. The research protocol was approved by the Institutional Review Board of Beaumont Research Institute. Written informed consent will be obtained from all participants.

All inpatients 18 years of age and older that require midline catheter placement by the bedside vascular access team will be eligible participants. Patients will be excluded if: Do not meet inclusion criteria 2. Multiple lumens required 3. Alternative diameter of catheter used 4. If already enrolled once prior 5. Withdraw voluntarily from the study 6. Are receiving oral, intravenous, or subcutaneous treatment dose anticoagulation (prophylaxis with anticoagulant is permissible).

Research staff of Beaumont Health Institute will allocate two midline catheters to eligible participants according to a pre-generated randomized list at a 1:1 ratio in block randomization to AngioDynamics BioFlo or Teleflex Arrowg+ard Blue Advanced midline catheters. Participant enrollment will take place from November 2018 until patient recruitment is complete. Demographic and health-related information will be obtained from electronic medical records during enrolled period at William Beaumont Hospital.

Practitioner Participation/Training

Advanced Practice Providers within the bedside PICC/Midline service at the Royal Oak campus are eligible to place catheters for this study. A cohort of fifteen providers are possible volunteers to be trained to place catheters for this study. Placing catheters for this study is not required and will be carried out on a strictly voluntary basis. All advanced practice providers are credentialed in placing PICCs and midlines by institutional policy and have greater than one year of experience in these procedures. None of the providers have previous experience with the Teleflex Arrowg+ard Blue Advance midline catheter. The clinical team from Teleflex will be expected to develop an educational/training pathway for providers to achieve proficiency prior to subject recruitment. A possible training/credentialing pathway may consist of: 1 hour didactic training followed by phantom training on a vein block and required successful placement of 2-4 catheters on real patients.

Initial Assessment

After written informed consent is obtained, investigators will carry out additional evaluation at the bedside. The research team will capture and save images of vessel depth and vessel diameter in short axis using the Sonosite S1 ultrasound equipment. Ultrasound guidance will be used for the initial assessment and procedure. The high frequency linear array transducer will be used for all procedures. Inserters will evaluate the vessel for valves, thrombosis, trajectory, and collapsibility per routine care. If the vein is appropriate for cannulation, the practitioner will continue with the procedure. Post-cannulation and post securement, functionality is confirmed with blood sampling (10 cc) and flush without resistance.

The research team also will document practitioner details, the vascular access device (VAD) used, the time of VAD placement, number of attempts, need for a rescue inserter, the vein that was cannulated, depth and diameter of the vein, and the indication for VAD placement. An attempt is defined as each time the needle punctures the skin. Data will be collected from the electronic medical record and includes: age, gender, BMI, vital signs, relevant past medical history. Specific medical history of interest includes: 1. VTE 2. Cancer (within past 6 months) 3. Hypercoaguable state 4. Current pregnancy/up to 8 weeks postpartum 5. Major surgery/major trauma within past 4 weeks 6. Estrogen supplementation 7. Long

travel > 6 hours within past 4 weeks 8. Inflammatory Conditions (IBD, SLE) 9. Immobilization >72 hours 10. Other. Indication for catheter placement will also be recorded: 1. DIVA 2. Antibiotics 3. Incompatible Medications 4. Other

Follow-up Assessment

Investigators will perform a follow-up assessment on all catheters within 24 hours of insertion and then daily for the life of the VAD. Generally all follow-up evaluations will occur between 8 am and 10 am. At each follow-up interval, the researcher will document the time of evaluation and assessment of functionality as well as review the patient chart for signs and symptoms of catheter-related bloodstream infection and document the presence of localized site infection. A catheter is functional if the investigator is able to withdraw 3-5 ml of blood or if the VAD flushes without resistance with 5 mL of saline. Even if the line is actively infusing upon evaluation, the investigator will stop the infusion and assess for functionality by drawing blood and flushing. Data specific to blood sampling will be collected daily. If the catheter was identified to have failed during follow-up assessment the date and time of failure and the reason for failure will be documented. If the catheter failed or was removed prior to the follow-up assessment then the VAD failure time and the assessment of failure and reason for line removal will be obtained through chart review. For all failed catheters, re-insertion attempt data will be tracked through the medical record in the nursing section for venous lines and need for reinsertion of the midline or escalation to a PICC, or CVC will be noted. If the patient is discharged prior to the time of follow-up assessment then the time of discharge will be documented and the VAD will be presumed functional until time of discharge unless otherwise noted in the chart.

Some patients may leave the hospital with the midline in place for additional intravenous therapies. If the patient is discharged with the midline, the research team will discuss the infusion plan with the care management team. Patients will also be provided detailed contact information of the Vascular Access Team (standard practice) at the time of hospital discharge in case any questions or complications arise. If the patient develops any concerning signs or symptoms for the venous thromboembolism, the Vascular Access Team will instruct the patient to return to the outpatient clinic for an evaluation with a member of the Vascular Access Team, schedule an urgent appointment with the medical doctor, or check into the Emergency Department for further evaluation. The research team will document imaging results from these encounters. All patients will receive follow-up phone call assessments by the research team. Patient disposition options include: discharge home/residence or to a skilled nursing facility or transfer to another hospital. If the patient is discharged home, infusion and catheter care occurs via home care or at an infusion center. For patients discharged to a skilled nursing facility, catheter care and infusion is managed by nursing staff at these centers. These patients will continue to be followed in the post-hospital setting, specifically to assess for the complication of thrombosis. The research staff will follow-up via telephone call with staff managing the infusion within 48 -72 hours of discharge and weekly including the last day of therapy to inquire about the VAD site and function of the catheter and document any complications/results to radiographic imaging. Once therapy is completed and the catheter is removed, the research team will follow up with the patient or designated legally authorized representative/next of kin via phone to inquire about the access site at 30 days post

line removal. All patients will receive the 30 day follow-up phone contact. Patients will specifically be asked if they developed redness, swelling, or pain at the catheter insertion site and had radiographic evaluation for a blood clot or pulmonary embolism. If the patient has a concern, the research team will forward the concern to Dr. Bahl and Emily Diloreto for further evaluation per routine.

SVT and DVT rates will be calculated based on upper extremity proven diagnosis of SVT and/or DVT in symptomatic cases. Researchers will review all study subject records in EPIC, the electronic medical records system, and screen enrolled subject data for all upper extremity venous Doppler examinations. Radiology interpretations will be reviewed for findings consistent with CR-UEVT. This review will occur thirty days post patient discharge. Symptoms and rationale for imaging will be documented. This information will be obtained by reviewing the order/provider documentation in EPIC. If the patient is diagnosed with thrombophlebitis, the location of the thrombus will also be documented.

Infection rate will be tracked using confirmed catheter-related blood stream infection data from the surveillance team within the epidemiology department. The team utilizes the CDC definition of laboratory-confirmed blood-stream infection (LCBSI). See Appendix A for LCBSI definitions and pathway for diagnosis.

The medication administration record will be queried for all medications given through each catheter. Vesicants that are generally given via central line or considered caustic to the vessel will be noted in both groups. Number of doses will be recorded. See Appendix B for full list of non-neoplastic vesicants. We will also collect data on patients that received alteplase for occlusion. We will specifically evaluate the relationship of alteplase use and how it relates to catheter-related thrombosis, catheter-related bloodstream infection, and functionality of catheter.

Sample Size and Statistical Analysis

Sample Size: For this randomly allocated, two group experiment, the primary outcome was complication profile in terms of thrombophlebitis. Under Aim 1, based on the preliminary analysis using approximately 13 months of data at William Beaumont Hospital, it suggested the incidence of thrombosis between 12-15% from 1,200 insertions of AngioDynamics BioFlo midline catheters with the diagnosis of symptomatic thrombosis. We established a one-sided Fisher's exact two-proportions test with a type I error $\alpha = 0.05$. In terms of results from previous study [1], sample size was designed to have a power of 80% for detecting a 11% lower in the incidence of thrombosis using Teleflex Arrowg+ard Blue Advanced midline catheters. Based on these criteria, 212 participants will be randomly allocated to 2 study groups (106 per group). This sample size included a 20% buffer to account for potential sample loss. For Aim 3, this sample size has a power of 0.85 to detect a hazard ratio of 1.5 for failure of functionality association with AngioDynamics BioFlo midline catheters, based on a log rank test with a 0.05 one-sided significant level and median time of midline catheter introduction into a vein of 10 days [1]. All above calculations were made using the power software PASS 16.

Statistical Analysis: For Aim 1 and Aim 2, we will use descriptive statistics (frequency, percent) to summarize the incidence of complication profile in terms of thrombosis and infection between these two groups. For Aim 1, a logistic regression model will be built to examine the association between midline catheters and the presence of thrombosis, adjusting for participant characteristics. The odds ratio (OR) associated midline catheters on thrombosis will be estimated. For Aim 2, we will further create cases of bloodstream infection per 1000 catheter-days,

accounting for catheter dwell times. A Poisson regression model will be employed to assess the relative risk (RR) of AngioDynamics BioFlo and Teleflex Arrowg+ard Blue Advanced midline catheters on the presence of infection within any observed catheter dwell time, adjusting for participant characteristics. P-values of less than 0.05 will be considered statistically significant. In addition, for Aim 3, we will create data with the first episode of function failure of catheter on IV treatment. To adjust for any difference in participant characteristics, Cox proportional hazard models will be built. We will evaluate the proportional hazard assumption for each fixed covariate of participant characteristics by the log baseline cumulative hazard plot, Schonfeld residual plot, and the interaction between the covariate and function time of midline catheters. If the assumption is violated, a stratified Cox proportional hazard model will be built. Hazard ratio (HR) of two midline catheters for function failure will be reported.

Site

William Beaumont Hospital, Royal Oak (RO) campus is a 1,100 bed major academic and referral center with Level 1 adult trauma and Level 2 pediatric trauma status. A major teaching facility, Beaumont, Royal Oak has 55 residency and fellowship programs with 454 residents and fellows. Beaumont is the exclusive clinical partner for the Oakland University William Beaumont School of Medicine. The Beaumont Research Institute was established more than 30 year ago at Royal Oak and offers research support services to clinical investigators.

Primary Investigator

I have specialized training in emergency ultrasound and completed fellowship in the field in 2008. Since that time, I have served as Director of Emergency Ultrasound for Emergency Medicine. I also serve as the Medical Director for the hospital vascular access team. Additionally, I have a specific interest in ultrasound-guided vascular access with several peer-reviewed publications and national presentations in this area.

References:

Lisova K et al. The incidence of symptomatic upper limb venous thrombosis associated with midline catheter: Prospective observation. Journal of Vascular Access. 2018. Epub ahead of print.

Klungboonkrong et al. Predictors of deep vein thrombosis associated with midline venous catheter in hospitalized patients: a single-institute experience. Journal of Vascular and Interventional Radiology 2015. 26(2) S146.

Gorski L et al. Development of an evidence-based list of noncytotoxic vesicant medications and solutions. J Infus Nurs. 2017;40(1)26-40

National Healthcare Safety Network (NHSN) Patient Safety Component Manual. Center for Disease Control. Chapter 4. 2018

https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf

Appendix A

Table 1: Laboratory-Confirmed Bloodstream Infection Criteria:
Must meet **one** of the following LCBI criteria:

Criterion	*Comments and reporting instructions that follow the site-specific criteria provide further explanation and are integral to the correct application of the criteria.* Once an LCBI determination is made, proceed to the MBI-LCBI definitions and determine if the corresponding MBI-LCBI criteria are also met (for example, after meeting LCBI 2, investigate for potential MBI-LCBI 2)
LCBI 1 If LCBI 1 criteria is met, consider MBI-LCBI 1	Patient of any age has a recognized pathogen, which is an organism not included on the NHSN common commensal list, identified from one or more blood specimens obtained by a culture or non-culture based microbiologic testing method (excluding organisms identified by testing on sera) **AND** Organism(s) identified in blood is not related to an infection at another site (See Appendix B: Secondary BSI Guide). **Notes:** 1. If a patient meets both LCBI 1 and LCBI 2 criteria, report LCBI 1 with the recognized pathogen entered as pathogen #1 and the common commensal as pathogen #2. 2. No additional elements (in other words, no sign or symptom such as fever) are needed to meet LCBI 1 criteria; therefore, the LCBI 1 DOE will always be the collection date of the first positive blood specimen used to set the BSI IWP.
LCBI 2 If LCBI 2 criteria is met, consider MBI-LCBI 2	Patient of any age has at least ***one*** of the following signs or symptoms: fever (>38.0°C), chills, or hypotension **AND** Organism(s) identified in blood is not related to an infection at another site (See Appendix B: Secondary BSI Guide). **AND** The same NHSN common commensal is identified by a culture or non-culture based microbiologic testing method, from two or more blood specimens collected on separate occasions (see Blood Specimen Collection). Common Commensal organisms include, but not are not limited to, diphtheroids (*Corynebacterium* spp. not *C. diphtheria*), *Bacillus* spp. (not *B. anthracis)*, *Propionibacterium* spp., coagulase-negative staphylococci (including *S. epidermidis)*, viridans group streptococci, *Aerococcus* spp. *Micrococcus* spp. and *Rhodococcus* spp. For a full list of common commensals, see the Common Commensal tab of the NHSN Organisms List.

Notes:

1. Criterion elements must occur within the 7-day IWP (as defined in Chapter 2) which includes the collection date of the positive blood specimen, the 3 calendar days before and the 3 calendar days after.
2. The two matching common commensal specimens represent a single element for use in meeting LCBI 2 criteria and the collection date of the *first* specimen is used to determine the BSI IWP.
3. At least one element (specifically, a sign or symptom of fever, chills or hypotension) is required to meet LCBI 2 criteria; the LCBI 2 DOE will always be the date the ***first*** element occurs for the first time during the BSI IWP, whether that be a sign or symptom or the positive blood specimen.

	6/1	Fever > 38.0 °C	**LCBI 2 DOE = 6/1**
	6/2	No LCBI element	
	6/3	No LCBI element	
Single element	6/4	*S. epidermidis*(1 of 2)	**Date of 1st diagnostic test = 6/4**
	6/5	*S. epidermidis*(2 of 2)	
	6/6	No LCBI element	
	6/7	No LCBI element	

Appendix B

RED LIST Well-recognized vesicants with multiple citations and reports of tissue damage upon extravasation	YELLOW LIST Vesicants associated with fewer published reports of extravasation; published drug information and infusate characteristics indicate caution and potential for tissue damage
Calcium chloride	**Acyclovir**
Calcium gluconate	**Amiodarone**
Contrast media - nonionic	**Arginine**
Dextrose concentration ≥ 12.5%	**Dextrose concentration ≥ 10% to 12.5%**
Dobutamine	**Mannitol ≥ 20%**
Dopamine	**Nafcillin**
Epinephrine	**Pentamidine**
Norepinephrine	**Pentobarbital sodium**
Parenteral nutrition solutions exceeding 900 mOsm/L	**Phenobarbital sodium**
Phenylephrine	**Potassium ≥ 60 mEq/L**
Phenytoin	**Vancomycin hydrochloride**
Promethazine	
Sodium bicarbonate	
Sodium chloride ≥ 3%	
Vasopressin	

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