TITLE:

UPPER ARM VS. FOREARM PLACEMENT OF EXTENDED DWELL CATHETERS: A COMPARATIVE EVALUATION OF BLOOD SAMPLING AND FUNCTIONALITY

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Study Protocol and Statistical Analysis Plan

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Background:

Nearly all hospitalized patients require intravenous (IV) access for treatment. Patients rely on functional vascular access to receive life saving IV therapies. Generally, peripheral IVs have high failure rates with 19-25% of IVs failing prior to completion of therapy and 45-56% of ultrasound-guided peripheral IVs failing prior to completion of therapy. Dislodgment, infiltration/extravasation, and phlebitis are common complications that lead to early failure. [1-5]

Many patients require ongoing blood draws or phlebotomy for laboratory testing during hospitalization. Hospitals generally avoid phlebotomy from peripheral IV catheters because they have been associated with increased rates of inaccurate laboratory testing and can increase dislodgment, infiltration, and phlebitis complications.[6] Patients are subjected to multiple needlesticks for blood sampling causing patient dissatisfaction and anxiety.[7] Further, health care workers are exposed to blood borne pathogens as blood draws can cause needlestick injuries.[8]

Extended dwell catheters (EDC) offer a viable alternative to peripheral IVs, especially for patients with prolonged hospital stays. EDCs are peripheral venous access devices placed under ultrasound guidance that are most commonly placed in the basilica, brachial, or cephalic veins and can be inserted above or below the antecubital fossa. These catheters can be left in place for up to 30 days and have an improved survival profile when compared to peripheral IVs.[9.10] While there is limited evidence on blood draw ability from these catheters, EDCs can be accessed for routine blood draws and potentially eliminate the need for additional needlesticks.

There is very limited research evaluating the impact of IV placement site on functionality or blood sampling ability. Only one small study of ultrasound-guided IV placements evaluated site in a prospective comparative fashion. The comparison was limited to evaluation of 56 patients in the “distal” or forearm group which comprised insertions in the antecubital/forearm area and 95 patients in the upper arm site. The authors concluded that “distal” placements have improved survival.[11] Further research is necessary to draw conclusions about EDCs and functionality/blood draws.

The potential value of forearm placements is especially relevant for patients with renal insufficiency. In the past three decades, there has been a significant increase in the patient population with chronic kidney disease. As the renal disease may progress and patients may require dialysis and establishment of an arteriovenous fistula, it is necessary to preserve the vasculature of the upper arm.[12]

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In summary, there is a gap of knowledge on EDCs and blood draw ability regardless of site of insertion. While survival of EDCs has been evaluated, there is no literature that compares survival of upper arm to lower arm placement.

Hypothesis/Objectives:

We hypothesize the forearm is the favorable site for ultrasound-guided IV establishment in terms of survival. Placement of the catheter in the forearm to avoid antecubital fossa or muscle bellies of the upper arm reduces kinking and involves insertion in more shallow vessels and likely enhances survival of the catheter.

We hypothesize the forearm provides similar blood sampling functionality compared to upper arm insertion.

We aim to quantify the difference in blood draw ability and catheter survival, comparing placement of an extended dwell catheter in the upper arm to the forearm.

Specific Aims:

Specific Aim 1: To compare upper arm versus forearm extended dwell catheter placement for blood sampling functionality.

For Aim 1, blood sampling ability of the forearm compared to upper arm will be evaluated by daily blood draws prior to patient discharge. The event is failure to aspirate blood during follow-up assessment during hospitalization.

Specific Aim 2: To compare upper arm versus forearm extended dwell catheter placement for dwell time/survival of catheter.

For Aim 2, an improved survival of the forearm placed catheter will be evaluated by functionality of catheter for intravenous therapy prior to patient discharge. The event is failure of functionality identified as inability to infuse without resistance during follow-up assessment during hospitalization. Duration of dwell and functional failure of the catheter will be employed to estimate catheter survival.

Specific Aim 3: To compare upper arm versus forearm extended dwell catheter placement for symptomatic catheter-related upper extremity venous thrombosis (CR-UEVT).

For Aim 3, we will measure incidence of all symptomatic CR-UEVT inclusive of superficial thrombophlebitis (SVT) and deep venous thrombosis (DVT) confirmed

by upper extremity venous duplex evaluation, to assess for a difference in thrombosis when an EDC is placed in the forearm compared to the upper arm.

Study Design

We propose a single-site, prospective two-arm randomized investigation of blood sampling and catheter survival of extended dwell catheters when site selection is evaluated. Specifically, EDC insertions in the forearm will be compared to upper arm insertions. The primary objective of this study is to demonstrate that blood sampling of the forearm (experimental group) is not inferior to blood sampling of the upper arm (control group). Exploratory secondary and adjusted multivariable analyses will also be conducted.

A single lumen, 20 gauge 8 cm EDC (BARD Powerglide ST™ Midline Catheter) will be utilized for this evaluation.

We aim to recruit 96 patients with 48 in each arm to assess blood sampling functionality.

Study Population and Eligibility:

A cohort of clinicians are proficient in ultrasound-guided vascular access at our hospital. In the emergency department (ED), several physicians and nurses are competent in the procedure. On the inpatient side, the Vascular Access Team (VAT) at our hospital receives daily consults for patients that have advanced vascular access needs. This includes patients with prolonged vascular access needs and/or difficult vascular access patients. All inserters are trained to place a number of catheters with ultrasound-guidance: peripheral IVs, midlines, and EDCs.

Eligible inpatient participants include: 1. Consult to VAT for vascular access device placement 2. Patient requires peripheral access. 3.18 years and older. Eligible ED patients include 1. 18 years and older 2. Difficult vascular access and anticipated hospital admission. Difficult vascular access is defined as: 1. Patient with no visible veins (>2 mm) or palpable veins in the upper extremity. Patients will be excluded if: 1. Multiple lumens required 2. Existing functional vascular access device proximal to the targeted area of insertion. This does not include superficial non-ultrasound guided peripheral IVs. 3. Upper extremity cannot be accessed due to a coexisting medical condition. 4. Cognitively impaired.

Patients meeting inclusion criteria will be consented and randomized by research staff to either upper arm or forearm insertion. If the inserter has no adequate target visualized in the randomly selected site, the inserter may evaluate another site that

is more suitable for cannulation. The site of insertion will be recorded and pertinent information will be collected similar to other enrollments.

Practitioner Participation/Training

Advanced Practice Providers (APP) within the VAT and ED practitioners proficient in ultrasound-guided vascular access at the Royal Oak campus are eligible to place catheters for this study. Participation in this study is not required and will be carried out on a strictly voluntary basis. Providers have limited experience with the BARD Powerglide ST™ Midline. The clinical team from BARD 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 +/- insertions on real patients. Once trained, providers can train the other providers.

Initial Assessment

Post-consent, eligible patients will be randomly allocated to the experimental group (forearm) or the control group (upper arm) in a ratio of 1:1 via a computer-generated randomization schedule. Research staff at the Department of Biostatistics will perform concealed immediate assignment by following a block scheme. Sealed envelopes containing the randomized IV access arm will be revealed at the bedside.

After patient enrollment, the inserter is engaged to perform the procedure. Only providers that are credentialed in ultrasound-guided vascular access will place catheters in study subjects. The research team will capture and save images of vessel depth and vessel diameter in short axis using the Sonosite or Mindray 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. A neutral pressure needle-free IV connector (One-link by Baxter Medical) will be connected to all lines. If the patient is randomized to the control group, the research staff will direct the inserter to choose either the basilic, cephalic or brachial vein at least 2 cm above the antecubital fossa. If the patient is randomized to the experimental group, the research staff will direct the inserter to place the catheter into the forearm at least 10 cm away from the antecubital fossa to ensure the distal tip of the catheter does not terminate in the antecubital fossa. The cephalic and basilic veins are typically cannulated in the forearm. If no adequate target is visualized in the randomly selected site, the inserter may evaluate another

site that is more suitable for cannulation. The site of insertion will be recorded and pertinent information will be collected similar to other enrollments.

The research team also will document practitioner details, the time of EDC placement, number of attempts, need for a rescue inserter, the vein that was cannulated, catheter to vein ratio, and the indication for EDC placement. Data will be collected from the electronic medical record and includes: age, gender, BMI, vital signs, relevant past medical history for difficult vascular access, and number, type, and site of previous vascular access devices during the current admission. The medication administration record will be queried for all medications given through each catheter. Specific attention will be given to vesicants listed in Appendix A. All upper extremity venous doppler imaging reports will be reviewed for thrombosis.

Follow-up Assessment

Investigators will perform a follow-up on the catheters daily while hospitalized. If qualified staff is not available, chart review will be performed on the first day staff returns back to the hospital. At each follow-up interval, the researcher notes the time of evaluation and assesses for blood sampling and functionality. At our institution, midlines and central lines can only be accessed for blood draws with a physician order. These instances are tracked in the medical record and will be recorded. The hospital policy for blood sampling follows Lippincott procedures for central venous access catheter blood sampling available at procedures.lww.com. If the qualified staff is able to aspirate blood from the catheter, blood sampling is considered intact. This sampling should be followed immediately by a 5-10 cc flush of saline to ensure no blood is visible in the tubing system. If blood does not readily aspirate, the line is flushed with 10 cc of saline and blood draw is re-attempted. If the catheter is unable to aspirate blood, the date and time of the failure of blood sampling is recorded. The presence or absence of blood within the lumen proximal to the hub is noted for occlusion for all VADs that cannot aspirate blood. After accessing the catheter, researchers are expected to flush and clean the catheter hub per institutional protocol for care and maintenance. All practitioners are given written instructions on this protocol. General functionality is also recorded if the VAD flushes with 5 ml of normal saline without resistance after the blood draw attempt. If the catheter cannot be flushed, the date and time of failure are recorded. If the catheter is identified to have failed prior to the follow-up assessment the date and time of failure and the reason for failure is obtained from chart review. If the patient is discharged prior to the time of follow-up assessment then the time of discharge is documented and the IV is presumed functional until time of discharge unless otherwise noted in the chart.

Sample Size and Statistical Analysis

The sample size for the proposed work is based on the first aim since the other aims will use the same samples. We determined the sample size for the proposed study based on the assumption that upper extremity catheters have successful blood sampling 50% of the time and clinically acceptable practice of 75% success applies to the experimental arm. If there is a true difference in favor of the experimental group of 25%, then 48 patients are required to be 95% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favor of the control or upper arm group of more than 20%. Considering dropout rate and early discharge, we doubled the sample size to 96 patients. When evaluating volumes of midline catheters placed at our institution, this is a feasible number of patients to recruit over 4-6 months.

Initial analyses will include descriptive statistics for all outcomes using means, standard deviations, and ranges for continuous measures, and frequencies and percentages for categorical measures. We will compare demographic and other potential confounding variables between arms using either Pearson's chi-square test (dichotomous variables such as gender) or a two-sample t-test (continuous variables such as age), as appropriate. Aims will be assessed using survival analysis with Kaplan-Meier curves, Pearson's chi-squared test, and logistic regression.

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.

Principal 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. Further, since 2016 I have functioned as the Medical Director for inpatient VAT. Additionally, I have a specific interest in ultrasound-guided vascular access with several peer-reviewed publications and national presentations in this area. Specifically, I have conducted and published prospective randomized

controlled trials investigating survival of intravenous devices. My CV is included for further details.

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Appendix A

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	