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A Randomized Trial Examining Plasma Exchange using the BD Catheter In an Outpatient Apheresis Unit (REPLACE)

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Introduction and Purpose

Nurses and apheresis technicians caring for patients requiring therapeutic apheresis procedures (TAP) utilize a wide range of intravenous catheters to obtain the access required to perform their procedures(Kalantari, 2012), (Golestaneh & Mokrzycki, 2013). The standard of care for our facility is to use an 18-gauge apheresis needle (Medisystems®) for the access site and an 18-gauge autogard catheter for the return site. Unfortunately, there is minimal literature defining best practices for catheter size selection(Salazar et al., 2017). At UT Southwestern Medical Center, our goal is to provide peripheral therapy to reduce the need for central access, such as a medical ports or tunneled catheters(Spires et al., 2018). However, the requirement for an 18 gauge catheter for an adequate return site, at times, rules out the patient for peripheral therapy(Putensen, Leverett, Patel, & Rivera, 2017). This requires central venous access to be obtained, which can delay the start of the procedure.

The lack of scientific evidence to support the use of smaller peripheral return catheters has increased the use of implanted ports in our institution(Putensen et al., 2017). The objectives of our pilot study are patient-centered and include analyzing the safety of using smaller peripheral return catheters without increasing the risk of hemolysis.

Background and Significance

TAP treats a wide range of disease processes and, in all cases, requires inlet and return venous access to perform the procedure. The goal of TAP is to return the patient to baseline and maintain independence and function. A larger needle (18 gauge) can cause more discomfort to the patient as well as additional scarring. A smaller needle may present less discomfort and scarring to the patient. Our goal in our outpatient clinic is to minimize disruption to the patient's routine and help them maintain normal activities of daily living.

To accomplish these goals, our outpatient clinic is open Monday thru Friday offering 4 different appointment times. All patients that are referred to our clinic for TAP, first receive a vein evaluation to see if the patient is a candidate for peripheral IV therapy. At our clinic, approximately 68% of our TAP's are performed peripherally. This eliminates the risk of a central line infection and any alteration in activities of daily living, such as bathing(Kramer, 2016), (Shang, Ma, Poghosyan, Dowding, & Stone, 2014),(Keller et al., 2018; McDiarmid, 2015).

Our hypothesis, is that the 20-gauge BD Nexiva Diffusics catheter provides the same efficacy as current practice with no increase in adverse events for patients undergoing therapeutic apheresis. The results from our study will be significant because if the 20 guage needle is equally effective for TAP, it can increase the number of patients that would be candidates for peripheral therapy. Therefore, decreasing the need for central venous access, which place the patient at an increased risk of infection. Our study is a comparison of 2 types of infusion catheters. The standard of care is an 18-gauge autogard catheter (control group) which will be compared to the 20-gauge BD Nexiva Diffusics (intervention).

P – patients who require therapeutic apheresis procedures (TAP)

I – use of 20G BD diffusics catheter during apheresis

C – use of 18 G standard of care IV catheter during apheresis

O – no difference in efficacy and no increase in safety events

Concise Summary of Project

This is a randomized pilot study of TAP using the current standard of care catheter (SOC) vs the BD Nexiva Diffusics Catheter. It is a single blinded, randomized study. Data will be used to refine and power a full randomized control trial. For this study, a sample of 33 encounters in each group (total of 66 encounters). Our specific aim is to test the hypothesis that the 20-gauge BD Nexiva Diffusics Catheter provides the same efficacy and lower pain level with no increase in adverse events for patients undergoing apheresis treatments.

Randomization Procedure

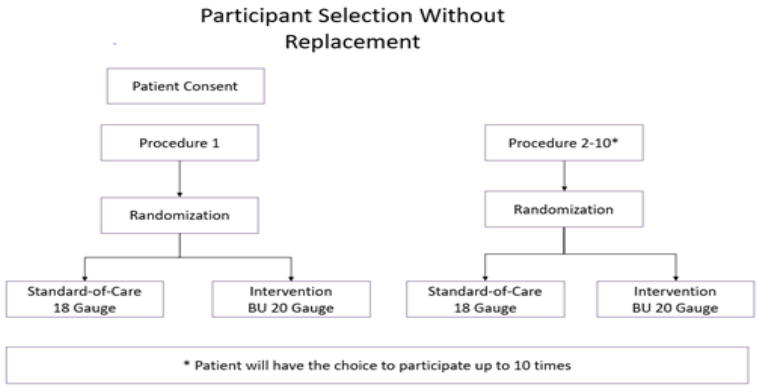
After an eligible participant is consented to the study the patient will be randomized without replacement to the use of one of the two catheters. Using a random number generator, numbers between (1-66) were randomly divided into two groups: SOC Control group and BD Intervention group (Figure 1). A study identification number (SID) key will be saved on a UTSW approved secure device and only the research coordinator will have access to the SID key showing which SID coordinates with each group. This will ensure that unblinding can occur is necessary and there is a backup to randomization.

The research coordinator will have 66 randomized envelops without replacement. Half of the envelops wil be assigned to 18G catheter SOC (control) and the other half be assigned to

20G BD Nexiva Diffusics catheter (intervention). The PI will be blinded, therefore the PI will pick an envelope when patients are consented and ready for treatment. Participants will be randomized after they have consented to the study. Participants' will then be randomized to one of the two groups again at each encounter (i.e., SOC visit). Inside the envelope it will tell the investigator if the patient is in the control or intervention group of the study.

To promote a more representative sample, each patient may participate a maximum of 10 times.

Figure 1. REPLACE study design



Study procedure:

Each enrolled patient will participate in the study will be randomized at each encounter. During each encounter the following information will be captured:

1. CBC
2. Patient discomfort level with placement of catheter
3. Inlet rate
4. Return line pressures
5. Procedures alarms
6. Procedure total time
7. Post procedure sample

Treating nurse (RN) will start the TAPs procedure with one of the 2 catheters. During the intervention period, the RN will be at bedside during as it is SOC in the Apheresis unit however for the purpose of this study the RN will have the study data collection form (DCF, Appendix1). The RN will complete the pre-assessment including a pain assessment to establish pain level prior to procedure that is currently documented in the electronic medical record. The patient will be asked to self-report the pain level after the return line has been started on the visual analog scale (VAS) Scale from 0mm to 100mm "0 being the lowest/ no pain, 100mm being the highest

level of pain". The VAS scale will be used for both the SOC and intervention group to compare the pain level when starting the return line. The RN will collect a CBC before the start of the procedure which will be used in the programing of the TAP procedure. The RN will start recording the "inlet rate, return line pressures, and alarms" every 15 minutes until the procedure is completed.

Before patient disconnects, and after the completion of procedure sing the same therapeutic apheresis procedure access site, a blood sample will be drawn by the RN 2 lavender top tubes (4ml) for plasma hemoglobin test. The plasma hemoglobin test will be sent to the UTSW lab for analysis of hemoloysis and results will be sent back directly to the PI. Blood sample results will be collected by the PI or the study team in an excel spreadsheet (CRF) that will be saved on a secure drive on the UTSW campus.

Hemolysis is defined as the destruction of red blood cells which leads to the release of hemoglobin from the red blood cells into the blood plasma. Each patient will be tested for hemolysis by running plasma hemoglobin test after the procedure has finished. This will be collected in a two lavender tops (4ml) The cost for this test is covered by sponsor and because the patient has an indwelling access to venous blood there will no charge for drawing the sample.. There is no clinical suspicion that the use of the 20-gauge BD Nexiva Diffusics Catheter will increase this risk. Hemolysis will be scored dichotomously as present or absent for each encounter.

Pain is defined as any increase discomfort experienced by the patient associated with the apheresis procedure. The current standard of care is to ask the patient "are you having pain" and then ask them to rate the pain from 0 to 10. For this study, one additional question will be asked after the patient's vein has been accessed (IV catheter in place). The patient will self-report their pain using a 100 mm VAS scale. "*The VAS has been used by healthcare providers to measure the characteristics of disease severity in each patient individually*"(Klimek et al., 2017) Currently, all peripheral apheresis patients have some pain/discomfort while having a treatment, however; it is usually tolerated with minimal complaints.

Measures of Quality of Apheresis will include inlet rate, and return pressures, procedure time. These measures are all readily available in the electronic medical record (EMR) and are all currently recorded as standard of care.

The inlet rate is defined as the percent of patient inlet rate divided by the maximum allowable inlet rate. Because inlet rates are different for each type of TAP has a different maximum inlet rate, this will allow standardization across procedures. The max inlet rate for Photopheresis is 50ml/sec, the max inlet for plasma exchange is 100ml/sec inlet for red blood cell exchange is 55ml/sec. In addition, the inlet rate for each participant in the intervention arm will be compared to the average of their last 5 procedures. This measure will compare the efficiency of the SOC verses the intervention.

Inclusion Criteria

- Adult (≥18 years old)
- Speaks and reads English
- A patient of the Apheresis clinic at UT Southwestern University Hospital and Clinics
- Scheduled to receive TAP (therapeutic plasma exchange, red blood cell exchange and extracorporeal Photopheresis) as standard of care

Exclusion Criteria

- Prisoners
- Persons under the age of 18 years
- Patient who are actively involved in chemotherapy

Sources of Research Material

There are three sources of data for this study: electronic medical record (EMR) and paper-and-pen data collection from the patient's bedside (Data Collection form), and lab results provided by the UTSW laboratory via EMR. The EMR data that will be collected will include demographic information such as: age, sex, race, ethnicity, and admission diagnosis. The paper-and pen-data collection will include the patient self-reported pain level (VAS Scale), CBC collection, procedure data (minutes, inlet rate, return line pressures and alarms) total procedure time and post procedure sample. The paper-and-pen data collection form (Appendix 1) will record data only during patients TAP's encounter. Blood sample will be obtained from a SOC line. An additional 8 ml's for blood will be drawn from the patients for research purposes. Results from the bloodwork will be provided by the UTSW laboratory via the patient's EMR.

Recruitment Methods and Consenting Process

For this study, patients will be recruited from the Apheresis Unit at UT Southwestern University Hospital and Clinics by a member of the research team. A member of the research team will screen the electronic medical record to determine a patient's eligibility. If a patient appears eligible for the study a member of the research team will discuss eligibility criteria with a member of the clinical team (nurse manger, nurse, physician, resident, fellow, social worker). The researcher will communicate with the clinical team to ensure eligibility: adult (≥18 years old), speaks and reads English, admitted to the Apheresis Unit at UT Southwestern University Hospital and Clinics at the time of consent. All patients in this study will be able to provide self-consent (read and speak English).

When a patient is deemed eligible, a member of the research team will discuss consent and study procedures with that patient, in a place that is comfortable for the patient. After being approached by a member of the research team, patients will have up to next visit to consider participation in the study. The study team expects recruitment of 30 participants to last approximately 8 months. (Table 1)

Potential Benefits

There may or may not be a direct benefit to the participants in this study. Any additional blood test result that seems out of the norm will be shared with the nurse on duty or treating physician. We would also hope to share this with the greater research and clinical community in hopes of finding an alternative way for apheresis patients to have therapeutic apheresis procedures with less pain and no increase in adverse events.

Potential Risks

Risks associated with BD Cather:

Longer procedure time might occur if the inlet rate of the treatment is slower. The patient will be informed of this during the ICF process. With smaller catheters there's a risk of not obtaining the appropriate return rate for the patient. When the return rate is out of the SOC parameters the SOC apheresis equipment (Optia or Cellex) will alarm. If the alarm sounds 3 times the RN will decrease inlet rate by 5 ml/sec until the minimum threshold is reached (if needed), which is 50 ml/sec for plasma exchange and 35 ml/sec for RBC exchange and 20 ml/sec for photopheresis. If the alarm continues to when the minimum threshold is reached the catheter will

be replaced with the SOC 18-gauge catheter. Obtaining blood samples may cause some discomfort, feeling lightheaded, fainting, bruising, clotting, and bleeding from the site of the needle stick and, in rare cases, infection. The risks are mitigated by drawing blood from a line that has already been established as part of SOC.

There is a low risk of breach in confidentiality. Subjects will be assigned individual study identification (SID) numbers and no personal identifiers will be included in the final summary.

Patients who are randomized to the 20-guage needle group and who fail the intervention will be given the 18-guage standard of care needle. At the patient's next visit, the patient will once again be randomized. If the patient is randomized into the 20-guage needle arm and fails the intervention a second time, the patient will be removed from the study.

Procedures to Maintain Confidentiality

Study participants will be given a study identification (SID) number. Only the approved study personnel and the principal investigator have access to the database linking the SID to the patient name. This database is kept on a protected drive on a password protected computer. Paper or hard copy participant records will be kept in a locked file cabinet in a locked office. If any identifying information is transmitted, it will be done so via secure e-mail and/or dedicated fax machines.

Statistical Analysis Plan

All data will be first collected on the DCF (Appendix I) and then entered into an electronic spreadsheet (e.g., MS Excel) which will be converted to SAS v 9.4 for analysis. All statistical analyses will be performed at UTSW in a location with secure data encryption capability. Initially, the data will be summarized first using standard measures of central tendency (mean, median, standard deviation, and interquartile range) for each variable. These will be examined to support the assumption of being approximately normally distributed. Baseline characteristics will be summarized using appropriate parametric and non-parametric measures.

The primary hypothesis is that the 20-gauge BD Nexiva Diffusics catheter provides the same efficacy of current practice with no increase in adverse events for patients undergoing therapeutic apheresis. This will be examined in 2 steps. First, ANOVA will be used to explore

efficacy wherein efficacy is represented by 1) the plasma hemoglobin value, and 2) the amount of time (minutes) required to complete a TAP. Hence models will be constructed to compare the mean plasma hemoglobin values by group, and to compare the mean number of minutes to complete TAP by group. Second, ANOVA will be used to compare the mean number of adverse events subjects experience in each group (intervention vs control).

Finally, a planned secondary analysis is to examine if the percent of lumen occupied by the return catheter is associated with return pressures. The suggested standard is that a catheter occupies < 45% of the inner-lumen diameter (measured with ultrasound). Return pressures >400 mm Hg are considered problematic. Chi-square analysis will be used to explore the odds of experiencing a return pressure > 400 mm Hg when the return catheter occupies <45% of the inner-lumen diameter.

Project Timeline

Item	Month 1-2	Month 3-6	Month 4-8	Month 9-11	Month 12-18
IRB approval	X				
Consent/ Enrollment	X	X			
Randomization	X	X	X	X	
Data collection	X	X	X	X	
Manuscript prep				X	X
Study closeout					X

Enrollment of first patient (month 1), enrollment of the last patient (month 12), completion of data analysis (month 14), and manuscript submission (month 18). The apheresis team see approximatley 3000 TAP treaments each year. Of these, approximately 1500 encounters will meet the primary inclusion criteria. We anticipate that it will take less than 1-year to complete the study.

Future directions

The intention of this pilot study is to test the 20-gauge BD Nexiva Diffusics Catheter performance and efficacy. The findings from this study will be used to provide additional preliminary data to BD to support a National Institutes of Health or Agency for Healthcare Research and Quality (AHRQ) application (pending 2017 AHRQ funding announcements). Stakeholder feedback will be provided through an optional de-identified report to all patients and families.

Presentation of data

It is anticipated that the results from this study will be presented to American Society for Apheresis at their annual convention. The results will also be summarized in a manuscript and submitted for peer-review publication to Journal of Clinical Apheresis.

Appendix 1

Patient Sticker

A **R**andomized Trial **E**xamining **Pla**sma Exchange using the BD **C**atheter In an Outpatient Aph**e**resis Unit
The "REPLACE" study

Date _____ SID _____ Procedure Type _____

Instructions:	Please complete the following form except for the VAS scale. Must be completed by patient to measure the characteristics of pain severity. Please circle option that apply.	
Collect CBC	**Yes**	**No**
Catheter type	**18 GA BD Autogard**	**20 GA BD Nexiva Diffusics**
Vein diameter w/tourniquet: _____	**Vein diameter w/o turniquet:** _____	**Vein diameter Procedure Running:** _____
Asses pain after return placement		
Please rate your current pain by drawing a vertical line across the bar below		

0 (mm) ——————————————— 100 (mm)

Not At All Severe — Extremely Severe

Procedure data

Procedure start time:

Minutes	Inlet rate	Return line pressures	Alarms	Comments

Total Procedure time:	Procedure end time:	Final Inlet Volume/Blood Processed:
Collect post proceduer **Plasma Hemoglobin**	**Yes**	**No**

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