t-PA Prophylaxis to Reduce Central Venous Catheter Associated Infection and Thrombosis (TOPCAT)

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Children's Hospital and Health System™

INSTITUTIONAL REVIEW BOARD
SUMMARY

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STUDY TITLE: t-PA Prophylaxis to reduce Central Venous Catheter Associated Infection and Thrombosis (TopCAT)

A. PURPOSE OF THE STUDY

The purpose of this pilot study is to test feasibility of concept, consent and enrollment rates, and mechanics of study designed to assess if intra-catheter dwells of tissue plasminogen activator (t-PA: Alteplase; Activase®, Genentech)is effective in decreasing the rate of clinically diagnosed central line associated blood stream infection (CLABSI) or venous thromboembolism (VTE) in central venous catheters (CVC) compared to standard of care heparin dwell.

B. HYPOTHESIS / SPECIFIC AIMS

We hypothesize there will be a lower rate of CLABSI or VTE in CVCs who receive t-PA as a dwell medication.

We will test this hypothesis in the following aims:

Aim 1: It is feasible to enroll patients with CVC and randomize to receive t-PA vs heparin dwell.

-Determine number of eligible patients, consents rates, and adherence to study protocol in patients with CVC in the CHW Intensive Care Unit (ICU).

-Calculate the number of centers needed to adequately power a multi-center trial to determine if t-PA is effective in reducing CVC complications from the rates found in this pilot study.

Aim 2: Compare the rate of VTE and CLABSI in patients with a CVC in the ICU randomized to receive t-PA vs. heparin as a dwell in the CVC.

-This will be a prospective, blinded, RCT enrolling 20 patients in the ICU with a CVC to receive t-PA or heparin to dwell for a minimum of 30 minutes every three days until CVC removal, discharge from the ICU or a maximum of 10 doses have been received.

C. BACKGROUND, SIGNIFICANCE, AND RATIONALE

Central line associated blood stream infection (CLABSI) and venous thromboembolism (VTE) continue to be a major source of morbidity in patients with central venous catheter (CVC). There is physiologic plausibility that by decreasing fibrin development with the use of t-PA in CVCs, the rate of CVC-associated VTE and CLABSI would be decreased.

It is well established that t-PA is safe and effective in restoring CVC patency after occlusion in adults (Deitcher 2002, Ponec 2001) and children (Blaney 2006), and is FDA approved for this use in both adults and children. Using t-PA for occluded CVC is standard of care in CHW PICU and is recommended by clinical practice standards, including Infusion Nurses Society (INS), Association for Vascular Access (AVA), American Association of Critical Care Nurses (AACN), Oncology Nursing Society (ONS).

It is not known if t-PA would be effective in preventing fibrin deposition and subsequent complications of VTE and CLABSI if administered prophylactically. Analysis of prophylactic t-PA used as a dwell solution for dialysis catheters suggests that this may be the case. A meta-analysis (Firwana 2011) reviewing randomized controlled trials of t-PA as a preventative locking solution for hemodialysis catheters compared to heparin found a decrease adverse events including thrombosis with the use of t-PA (Schenk 2000, Hemmelgarn 2011, Gittins 2007).

Use of t-PA for preventing VTE and CLABSI in the non-dialysis catheter is very limited. Preliminary evidence in pediatric patients with long term CVC dependency has shown that prophylactic dwell of tissue plasminogen activator (t-PA) has decreased episodes of CVC dysfunction; however, that study was underpowered to test the outcomes of CLABSI or VTE(Malec 2017). A multicenter study would be needed to provide sufficient sample size. The pilot study proposed here will test feasibility of concept, enrollment and consent rates, and mechanics of study design to be used to inform a grant application for a future multicenter trial.

Currently, heparin as a capping or locking solution is the standard of care for functioning CVCs at CHW with t-PA reserved for restoration of flow with occluded CVC.

D. DESIGN AND METHODS

This pilot study at CHW will be a prospective, blinded, RCT enrolling 20 patients in the PICU with a CVC to receive t-PA (study drug) or heparin (current standard of care and defined as control arm for this study) to dwell for a minimum of 30 minutes every three days until catheter removal or discharge from the PICU. Primary outcomes would be CLABSI or VTE. Secondary outcomes would be episodes of CVC dysfunction, off study use of t-PA, and bleeding.

Patients meeting the following criteria will be eligible for study participation

Inclusion criteria:

- Age >2 weeks(corrected for gestational age) to ≤ 18 years old

- PICU admission
- CVC placed within 72 hours of enrollment (tunneled such as PICC, Broviac or Hickman, or untunneled) and in place during hospitalization

Exclusion criteria:

- Pregnancy
- Non-English-speaking subjects and/or parent/guardian
- Platelet count < 20,000
- Active CVC infection-defined as positive blood culture from the in -situ CVC at time of enrollment
- Current radiographically confirmed VTE
- Currently receiving treatment doses of anticoagulation (heparin infusion >15U/kg/hr, enoxaparin injections >=2mg/kg/day or >=60mg/day)
- CVC diameter <1.9 Fr
- Current or previous diagnosis of Heparin Induced Thrombocytopenia or allergy to heparin or t-PA
- Med-a-port catheters
- Active internal bleeding
- Recent intracranial or intraspinal surgery
- Serious head trauma
- Intracranial conditions that may increase the risk of bleeding
- Bleeding diathesis
- Current severe uncontrolled hypertension

Any patient admitted to the ICU and meeting the above inclusion criteria will be approached for consent within 72 hours CVC placement. Randomization and administration of t-PA/heparin control treatment will be initiated within 24 hours of enrollment.

After 1:1 randomization, t-PA/heparin will be infused in the CVC for a dwell duration of 30 minutes-4 hours and then withdrawn (lock therapy) every 3 days until discharge from the PICU, CVC removal or a maximum of 10 doses received. Additional lumens will be treated on subsequent days. Any lumen requiring continuous infusion of vaso-active medication will not receive dwell therapy, evaluated on a day-to-day basis. Timing of instillation of study dwell medication will be adjusted so as not to interfere with medications for patient care. Other stopping points of t-PA treatment are in Section L.

E. TOTAL NUMBER OF HUMAN RESEARCH PARTICIPANTS PROPOSED FOR THIS STUDY AT THIS SITE AND GLOBALLY. WHAT ARE THESE NUMBERS BASED ON?

This single center, pilot study will enroll 20 subjects at CHW. This sample size was chosen for the ability to be internally funded and to complete pilot data collection in a timely manner, with anticipated grant submission for a multi-center study in 2020.

F. DRUGS OR PROCEDURES

Procedures to be completed for this study are as follows:

After informed consent/assent, the patient will be randomized and assigned to either the treatment arm (t-PA lock) or control arm (heparin lock). Randomization will be stratified by age (<5 or ≥5 years old). Pharmacy will blind the study medication t-PA so that it is indistinguishable from the control arm. Randomization will be done in the investigational pharmacy prior to the dispensing of the t-PA/heparin. During enrollment, the unblinded assignment log will be kept in the locked investigational room in central pharmacy.

Study Treatment and Dosing

In subjects randomized to the t-PA (Alteplase; Activase®, Genentech, 1mg/cc concentration), dosing will comply with the CHW Policy and Procedure Protocol *t-PA Administration for Central Venous Access Devices (CVAD)*; subjects randomized to the control arm, standard of care heparin group, will receive an equivalent volume for weight of heparin 10 units/ml. The bedside RN will administer the study medication/heparin as per the above protocol. The CVC should be flushed with normal saline prior to infusion of t-PA/heparin. After dwelling time of 30 minutes-4 hours, t-PA/heparin control should be withdrawn, check for blood return in CVC and flush line with normal saline as per policy. Each lumen of multi-lumen CVC should be treated every 3 days until patient discharge from ICU, removal of CVC, or a maximum of 10 doses of t-PA/heparin control are received.

Patient weight	Volume T-PA/Heparin
0-10kg	0.5ml
10-20kg	1 ml
>20kg	2 ml

These doses by body weight have been approved by the FDA for and CHHS Patient Care Protocol (tPA Administration for Central Venous Access Devices (CVADs) for use in children with CVC and are not associated with significant bleeding. If a 2mg (ml) dose of t-PA is administered by bolus injection directly into the systemic circulation, rather than as a dwell within the CVC, the drug concentration would return to endogenous levels with 30 minutes.

Ultrasound imaging

At the end of the study period, a noninvasive ultrasound with doppler will be performed for research purposes to assess for asymptomatic thrombosis in the blood vessel of the CVC location.

G. RISK CATEGORY:

Both arms of the study: Risk Level (2) 45 CFR 46.405 - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

H. RISKS AND THE PRECAUTIONS WHICH WILL BE TAKEN TO MINIMIZE RISK EXPOSURE

There is a risk of bleeding at higher doses of both the study drug (t-PA) and heparin control, as both drugs used in standard clinical practice alter the coagulation system. However, the doses by body weight used in this study have been approved by the FDA for and CHW Policy *tPA Administration for CVADs* for use in children with CVC and are not associated with significant bleeding. If a 2mg (ml) dose of t-PA is administered by bolus injection directly into the systemic circulation, rather than as a dwell within the CVC, the drug concentration would return to endogenous levels with 30 minutes. As a precaution, we will monitor the dose of drug received and follow the CHW policy and procedure for administration. Both arms of the study are currently used in clinical care, it is the timing of the intervention that is under study. As additional precaution, we will exclude patients at increased risk of bleeding (platelet count < 20,000 or receiving therapeutic dosed anticoagulation).

All adverse events experiencing by study subjects will be monitored throughout the active study treatment period and for 30 days following the last dose of the t-PA/heparin, or for 7 days after CVC removal, whichever occurs first. For patients with CVC in place at time of hospital discharge, chart review will be performed to capture events up to 7 days after discharge.

Breach of Confidentiality

Data necessary for the completion of this study will be extracted from the subject electronic medical record and maintained in a REDCap database on the CTSI server. Some PHI will be maintained in this database but will only be accessible to study team members listed on the registration page. Any study information maintain on paper will be held in a locked file cabinet in the Critical Care offices.

I. PROVISION FOR THE PROTECTION OF PRIVACY OF SUBJECTS AND TO MAINTAIN THE CONFIDENTIALITY OF DATA

As of October 2017, the NIH has updated their policy on Certificates of Confidentiality and are automatically issuing these for eligible studies that are NIH funded. They no longer issue a paper certificate, nor only submit on request.

Does this study qualify for automatic issuance of a Certificate of Confidentiality by the NIH?

☒No ☐Yes

The following encryption products employ cryptographic modules that the National Institute of Standards and Technology has certified as meeting FIPS 140-2 requirements. Children's Hospital and Health System endorsed the use of these products made to encrypt hard drives and removable media. All electronic research data must be encrypted using one or more of these products.

Please indicate which encryption tools you are using to secure your research data.

___Credent Mobile Guardian (RS, PD)

___GuardianEdge Hard Disk and GuardianEdge Removable Storage Encryption (HD, RS, PD)
___IronKey encrypted flash drives (RS)
___McAfee Endpoint Encryption (HD, RS)
___Microsoft Bitlocker (HD, RS when used with Windows 7 and FIPS compliant algorithms are enabled)
___PGP Whole Disk Encryption and PGP Portable (HD, RS)
___SafeNet Protect Disk and SafeNet Protect File (HD, RS)
___Seagate Secure Self-Encrypting Drives (HD when encryption option is enabled)
___Symantec Endpoint Encryption (HD, RS, PD)
___WinMagic SecureDoc encryption (HD) (for MCW owned computers)
___Other (*add description*)

Does not apply because:
___ Data is de-identified – no PHI collected (*please provide detailed information on data elements in your protocol application)*
___ Data is stored on paper only
___ Data is stored on CHW secured shared drives.
✓ Data is stored on MCW secured shared drives.

J. PROVISIONS FOR MONITORING DATA TO ENSURE THE SAFETY OF SUBJECTS; AND ADDITIONAL SAFEGUARDS TO PROTECT THE RIGHTS AND WELFARE OF SUBJECTS WHO ARE LIKELY TO BE VULNERABLE

Adverse Event Monitoring

Any patient receiving a minimum of 1 dose of the t-PA/heparin control will be followed for adverse events by the study investigators and research coordinators for 30 days following the last dose of the t-PA/heparin, or for 7 days after CVC removal, whichever occurs first. For patients with CVC in place at time of hospital discharge, chart review will be performed to capture events up to 7 days after discharge.

Adverse events will be considered any change from baseline. Expected adverse events are listed in section H; this section also includes those events considered serious but expected within this protocol. Expected SAEs will be reported in aggregate at the study's annual review. Any SUSAR experienced during the study will be reported per IRB's Reportable Events guidelines. At completion of the study adverse event rates between the study group and heparin control group will be compared and included in any final study reports.

Serious Adverse Events

If any subject enrolled in the study experiences any serious adverse event, the study team and care team will discuss the likely cause of the events. If it is determined that the event is probably or definitely related to the t-PA/heparin control the study treatment can be discontinued at the discretion of the care team and study team. Subjects whose treatment is discontinued will be followed for 30 days after the last t-PA/heparin control dose or until hospital discharge, whichever occurs first.

K. ANTICIPATED BENEFITS ASSOCIATED WITH THE PROTOCOL TO HUMAN RESEARCH PARTICIPANTS AND SOCIETY

Benefit to the individual patient may include a decreased risk of CVC infection or VTE.
Benefit to society at large will be knowledge gained to optimally design multicenter interventional study to develop therapy to reduce the risk of central line infection and/or thrombosis. There is evidence that these complications result in unfavorable outcomes such as increased length of mechanical ventilation, increased length of stay, increased healthcare cost, and increased mortality.

L. STOPPING POINTS THAT WOULD NOT ALLOW THE STUDY TO CONTINUE AS PROPOSED

Withdrawal from study

The PI or subject's primary care team can withdrawal the subject from this study due to

- Consent is withdrawn by subject's family
- Treating physician wishes to withdrawal subject for any reason

M. IS THERE A DATA SAFETY MONITORING BOARD IN PLACE? WHO ARE IT'S MEMBERS? HOW OFTEN DO THEY MEET?

There is no DSMB planned for this study.

N. DESCRIBE HOW THE CONSENT AND ASSENT PROCESS WILL TAKE PLACE. INCLUDE A LIST OF APPROPRIATELY TRAINED PERSONNEL WHO WILL BE INVOLVED.

After an eligible subject is identified, written informed consent will be obtained in person by an investigator or coordinator listed on the registration page for this study. Study investigators who are also the eligible subject's attending physician at the time of consent will not participate in the consent conversation to remove any undue influence posed by the duel role. Following consent, a copy of the completed documents will be placed in the subject's medical record, and a second copy will be given to the subject's family. A consenting and enrollment log will be maintained by the research team for all the patients who are screened for study, approached meeting eligibility criteria of the study and who consented/ or denied participation in the study.

We are requesting a waiver of assent for patients intubated, pharmacologically sedated, cognitively delayed that they would not fully comprehend what they are consenting to, and patients too critically ill defined as reduced consciousness or impaired decision-making capacity. The decision of an individual's capability to assent for the study is made by reviewing medical records for that specific information. This is always confirmed with attending physician for finalization of assent waiver for the study before patient is approached. Assent will be obtained from the patient if he/she is at least 7 years of age and is alert enough or cognitively able to understand the nature of the study. This assent will be obtained for all child subjects (7-17 years old) and documented by signing a separate assent form (for 7- 13 years old) or by signing an assent line on the parent permission form (for 14-17 years old). If the patient turns 18 years old while still participating in the study, we will have patient confirm his or her interest in continuing participation. If patient is still interested in study participation we will have him or her consent during the current admission.

We plan to enroll only English speaking patients for this 20 patient pilot study. We do not have available funds and resources at this time to provide Spanish ICF documents for this pilot study. If we notice a large population of Spanish speaking patients being excluded we will consider including Spanish Speaking patients in the next phase of this study after the pilot is completed.

O. PROCEDURES TO BE EMPLOYED IN ANALYZING DATA AND THE ANTICIPATED SIGNIFICANCE OF THE PROPOSED STUDY

Aim 1 Outcomes will include consent rates and determination of sample size to adequately power a multicenter trial to determine if t-PA reduces the rate of CVC complications (CLABSI and VTE) by 20%.

Aim 2 Outcomes

The primary outcome will be rate of clinical diagnosed CLABSI and VTE in each arm. Secondary outcomes will include: episodes of CVC dysfunction (defined as inability to draw blood from line and/or inability to flush CVC), off study use of t-PA, and clinical bleeding

Statistical analysis plan

Analysis will be performed by Quantitative Health Sciences under the direction of Dr. Pippa Simpson. Data will be investigated with summary statistics (e.g. frequencies, median and inter-quartile range). Where appropriate for a parametric analysis transformation will be used or a non-parametric analysis will be used. Differences between t-PA and heparin control groups will be examined by using Chi-square and Fisher's exact tests for categorical variables, and a Mann-Whitney test or a t-test for the continuous or ordered variables.

P. FINANCIAL RELATIONSHIPS

This study has received internal funding from the Department of Pediatrics, Medical College of Wisconsin. This funding will be used to pay for t-PA and completion of study procedures.

Q. ADVERTISEMENTS / FLIERS

No fliers or advertisements will be used to recruit subjects for this study

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