Feasibility of Tissue Plasminogen Activator Dwell Therapy to Reduce Central Venous Catheter Associated Thrombosis: A Randomized Controlled Pilot Trial

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Research Article

Keywords: Child, tissue plasminogen activator, central venous catheters, thrombolytic therapy, venous thrombosis, critically ill

DOI: https://doi.org/10.21203/rs.3.rs-847281/v1

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Abstract

Background: To evaluate the feasibility of a randomized controlled trial (RCT) of the fibrinolytic tissue plasminogen activator (t-PA) vs unfractionated heparin (UFH) central venous catheter (CVC) dwell therapy to reduce risk of CVC-associated deep venous thrombosis (CADVT) in critically ill children.

Methods: This single center quadruple blinded pilot RCT enrolled children ≤ 18 years of age with CVC placed within 72 hours of admission to the pediatric intensive care unit (ICU)

Weight-adjusted dose of study drug dwell (t-PA vs UFH) was installed to alternating lumen of CVC every 3 days for 10 doses, CVC removal or ICU discharge. Ultrasound with doppler was performed at study completion.

Main Results: Of 426 children screened from April-Dec 2019, 86 (20%) were eligible with 20 enrolled and randomized. Primary outcome measure of enrollment rate was 23%. One child was withdrawn immediately after randomization due to development of exclusion criterion. Secondary feasibility outcome measures were proportion of children who received study drug within 24 hours of consent (100%), proportion with ultrasound (100%), and proportion completing the study (95%). Eighteen of 19 children received the first dose within 48 hours of CVC placement. All children missed some dose days because of lumen specified to be in continuous use. Median dwell time for doses received was >2 hours. There were no protocol violations. Six of 19 patients (31.6%) developed CADVT, 1 of which was occlusive. There were no catheter-associated blood stream infection or significant bleeding.

Conclusion: Critically ill children requiring CVC are at high risk for CADVT. A future multicenter, blinded, RCT to determine the effectiveness of t-PA vs UFH dwell in reducing CADVT is feasible.

Registered August 10, 2018 on ClinicalTrials.gov NCT03672006

Key Messages Regarding Feasibility

- The ability to enroll children with CVC, and availability of CVC lumen for study drug dwells was unknown prior to this pilot study.
- Primary outcome of enrollment was 23%, with most frequent reason for lack of enrollment was family unavailability. 100% of enrolled children received study drug within 24 hours of consent, and 95% completed the study.
- A RCT to determine the effectiveness of t-PA vs UFH is feasible. Attention to off-hours study team availability for consent may improve enrollment rates.

Background

Venous thromboembolism (VTE), which mainly manifests as deep venous thrombosis (DVT), is a top contributor to harm and excess costs in hospitalized children.1,2 Critical illness and central venous
catheter (CVC) are the most important risk factors for DVT in children.\(^3\text{-}^5\) CVC-associated DVT (CADVT) can serve as a nidus of infection and increases the risk of CVC-associated bloodstream infection (CABSI).\(^6\) Tissue plasminogen activator (t-PA), a fibrinolytic enzyme, is an established therapy to restore CVC patency after dysfunction from intra-catheter thrombi.\(^7\text{-}^9\) For prophylaxis, t-PA infused to dwell in dialysis catheters is associated with lower risk of CADVT than unfractionated heparin (UFH) dwell.\(^10\text{-}^13\) t-PA may also prevent CADVT in non-dialysis CVC, but evidence is limited. t-PA dwell has only been shown to reduce the risk of CVC dysfunction in children with long term CVC dependency, as this study was underpowered to evaluate the effect of t-PA on CADVT or CABSI.\(^14\)

A multicenter, randomized clinical trial (RCT) is needed to determine the efficacy of t-PA in preventing CADVT in children. This pilot RCT aimed to test the feasibility of a RCT of t-PA dwell against CADVT in critically ill children.

**Methods**

**Study design**

This single center quadruple blinded RCT was approved by Children’s Hospital of Wisconsin Institutional Review Board (IRB# 1293254-5). The RCT was conducted from April to December 2019. Informed consent and assent, as appropriate, were obtained prior to starting any study procedures. Children were randomized 1:1 to t-PA dwell (treatment arm) or UFH dwell (control arm). Randomization was performed by the investigational pharmacist using a computerized algorithm. Participants, care providers and study team were blinded to assignment until after completion of analysis.

**Population**

All children admitted to the pediatric ICU with a CVC placed prior to or during admission to the pediatric ICU were screened for eligibility. Patients > 2 weeks post-gestational age to \(\leq 18\) years of age with a CVC placed within 72 hours of enrollment were included. Exclusion criteria were:

Non-English-speaking subjects and/or parent/guardian

Pregnancy

Active CVC infection; defined as positive blood culture from the in-situ CVC at time of enrollment

Current radiographically confirmed VTE

CVC diameter < 1.9 Fr

Current or previous diagnosis of heparin induced thrombocytopenia or allergy to UFH or t-PA

Med-a-port catheters or hemodialysis catheters
Currently receiving treatment doses of anticoagulation (UFH infusion > 15U/kg/h, enoxaparin injections ≥ 2mg/kg/day or ≥ 60mg/day)

Active internal bleeding

Recent intracranial or intraspinal surgery

Serious head trauma

Intracranial or other conditions that may increase the risk of bleeding

Coagulopathy or bleeding diathesis (includes platelet count < 20,000/mm$^3$, INR > 2.0)

Expected CVC removal within 48 hours

Expected transfer or discharge within 48 hours

Exclusion based on bleeding risk aligned with local criteria for administration of systemic t-PA.

**Study Drug**

Children randomized to treatment arm received weight-adjusted dose of t-PA (Alteplase; Activase®, Genentech, 1mg/mL concentration). Children weighing < 10 kg, 10–20 kg or > 20 kg received 0.5 mg (0.5 mL), 1 mg (1 mL) or 2 mg (2 mL) of t-PA, respectively. Children randomized to control arm received the equivalent volume per weight of 10 U/mL of UFH. The study drug was dispensed in indistinguishable syringes labeled with the child’s unique study ID.

**Study Procedures**

Within 24 hours after enrollment, the bedside nurse administered the study drug. The CVC was flushed with normal saline, then the study drug was infused, dwelling for 30 minutes to 4 hours. Dwells were stopped based on the clinical need for the lumen. Longer dwell times may be more efficacious but may not be practical due to clinical needs. After the dwell, the study drug was withdrawn, the CVC checked for blood return and then flushed with normal saline. Each lumen was treated, as possible, every 3 days until discharge from ICU, removal of CVC, or a maximum of 10 doses of study drug were administered. Study drug was not administered to lumens used for continuous infusion of vasoactive medication.

All children who received ≥ 1 dose of the study drug were followed for CADVT, CABSI and bleeding for 7 days after CVC removal, or for 30 days if the CVC remained in place.

For children with CVC still in place at the time of hospital discharge, medical records were reviewed to capture events up to 7 days after discharge. At the end of the study period, ultrasound with doppler was performed to assess for CADVT in the site of CVC placement. The reading radiologist was blinded to treatment assignment.

**Outcomes**
The primary outcome measure was enrollment rate defined as proportion of eligible children who were randomized. Secondary feasibility outcome measures were proportion of children who received study drug within 24 hours of consent, proportion with ultrasound, and proportion of enrolled patients completing the study. Other secondary outcomes for efficacy were CADVT as diagnosed by the systematic ultrasound, CABS as diagnosed by the clinical team, and CVC dysfunction defined as inability to draw or flush CVC, and for safety, any clinically overt bleeding.

**Statistical Considerations**

Baseline characteristics and outcomes were reported as a single cohort to avoid over-interpretation of unstable estimates from a limited sample size. Data was presented as median (interquartile range, IQR) for continuous variables and count (percentage) for categorical variables. A sample size of 20 was planned based on available resources.

**Results**

*Eligibility and consent*

A total of 426 children with a CVC were screened April-Dec 2019 (Fig. 1). Of these, 86 (20%) were eligible. The most frequent reasons for exclusion were expected CVC removal in less than 48 hours (N = 68) and concurrent receipt of therapeutic anticoagulation (N = 58). Of the eligible children, 30 (35%) were approached for consent. Lack of available parent/guardian was the most common reason for failure to approach for consent (N = 41). Enrollment rate was 23% of eligible patients. All consented patients were randomized. However, one child was excluded after randomization, but prior to receiving the study drug, because of immediate use of therapeutic anticoagulation. All other patients received the study drug within 24 hours of enrollment.

*Patient and CVC characteristics*

Median age of enrolled children was 6 years (IQR: 1.4, 11 years) (Table 1). Most had risk factors for VTE, such as vasopressor use (N = 16) and invasive or non-invasive ventilation (N = 16). Untunneled CVC (N = 16) was most common. Most CVC were placed in the upper extremity (N = 14).
Table 1  
Patient, Central venous catheter and study drug factors

| Patient factors                  | Patients N = 20 |
|----------------------------------|----------------|
| Age, years                       | 6 (1.4, 11)   |
| Weight, kg                       | 15.7 (8.1, 36.7) |
| Infant age                       | 4             |
| Diagnosis category               |               |
| Medical                          | 10            |
| Surgical                         | 10            |
| VTE risk factors                 |               |
| Ventilation                      | 11            |
| Invasive                         | 5             |
| Non-invasive                     | 4             |
| None                             |               |
| Vasopressor use                  | 16            |
| Neuromuscular blockade           | 7             |
| TPN                              | 5             |
| CRRT                             | 1             |
| RBC transfusion                  | 13            |
| Plasma transfusion               | 0             |
| Platelet transfusion             | 0             |
| Concurrent Anticoagulation       |               |
| Any anticoagulation              | 6             |
| LMWH                             | 2             |
| UFH < = 10u/kg/hr                | 1             |

Data presented as N or median (interquartile range)

t-PA-tissue plasminogen activator, CVC-central venous catheter, VTE-venous thromboembolism, TPN-total parenteral nutrition, CRRT-continuous renal replacement therapy, RBC-red blood cell, LMWH-low molecular weight heparin, UFH-unfractionated heparin, NSAID-non-steroidal anti-inflammatory, Fr-French, ICU-intensive care unit, OR-operating room, IR-interventional radiology, ED-emergency department
| **Patients N = 20** |  |
|---------------------|--|
| UFH > 10u/kg/hr     | 2 |
| None                | 14|
| Antiplatelet therapy|  |
| Aspirin             | 4 |
| NSAID               | 4 |
| **CVC factors**     |  |
| CVC type            | 15|
| Untunneled          | 5 |
| Others              |  |
| Sidedness           | 5 |
| Left                | 15|
| Right               |  |
| Size                |  |
| ≤4Fr                | 13|
| >4Fr                | 7 |
| **Anatomic site**   |  |
| Upper extremity     | 14|
| Lower extremity     | 6 |
| **Placement location** |  |
| ICU                 | 8 |
| Others (OR, IR, ED) | 12|
| CVC days in study   | 6 (3, 8.5)|
| **Study drug factors** |  |
| Day of 1st dose     | 1(0,2)|

Data presented as N or median (interquartile range)

t-PA-tissue plasminogen activator, CVC-central venous catheter, VTE-venous thromboembolism, TPN-total parenteral nutrition, CRRT-continuous renal replacement therapy, RBC-red blood cell, LMWH-low molecular weight heparin, UFH-unfractionated heparin, NSAID-non-steroidal anti-inflammatory, Fr-French, ICU-intensive care unit, OR-operating room, IR-interventional radiology, ED-emergency department
**Patients N = 20**

|                                |       |
|--------------------------------|-------|
| Total dose days, N             | 3 (2, 4) |
| Days missed dose, N            | 3 (1, 4.5) |
| No. of lumen treated, N        | 2 (2, 2) |
| Off label t-PA doses, N        | 0 (0, 1) |
| Dwell time, minutes           | 133.5 (86, 147) |

Data presented as N or median (interquartile range)

*t-PA*-tissue plasminogen activator, CVC-central venous catheter, VTE-venous thromboembolism, TPN-total parenteral nutrition, CRRT-continuous renal replacement therapy, RBC-red blood cell, LMWH-low molecular weight heparin, UFH-unfractionated heparin, NSAID-non-steroidal anti-inflammatory, Fr-French, ICU-intensive care unit, OR-operating room, IR-interventional radiology, ED-emergency department

**Study dosing**

Of the 19 children who received the study drug, 18 received the first dose within 48 hours of CVC placement as shown in Table 1. All children missed some dose days (median of 3) because of the lumen specified being in continuous use. The median dwell time for doses received was 133.5 minutes. No violations in study protocol, such as unblinding, administration of study drug into incorrect lumen, or timing of study exit ultrasound were reported.

**Outcomes**

Only aggregate results are presented as recommended for pilot RCTs. Six of 19 children (31.6%) developed CADVT, 1 of which was occlusive. There were no episodes of CABS1. Episodes of CVC dysfunction occurred in 7 CVC (36.8%). Most episodes were categorized as an inability to draw blood from a lumen. There were 5 non-major nor clinically significant bleeding events in the RCT. None required intervention.

**Discussion**

This pilot RCT has shown that a blinded RCT of t-PA vs UFH dwell to decrease the risk of CADVT in critically ill children is feasible, with 23% of parents of eligible patients agreeing to participate in the RCT and randomized within 72 hours of CVC placement. Fifty-six of the 86 eligible patients were not approached for consent. The most common reason (41/56) was lack of family availability. Of those approached, 67% consented to study participation. Expansion of research team availability in a future study to include nights and weekends may improve the enrollment rate. No violations in study protocol were reported. All children missed some doses of study dwell as lumens requiring continuous infusion of vasoactive medication did not receive study drug, which was pre-specified in the protocol.
This RCT was not designed nor powered to answer the question if t-PA is efficacious in reducing CADVT compared to UFH dwell in critically ill children with recent CVC placement. However, the results confirm that this is a population at risk for CADVT, with over 30% developing CADVT. Similarly, this RCT was not designed to determine safety. However, there were no clinically significant bleeding events. As expected, from the long history of using t-PA for CVC occlusion and UFH to maintain CVC patency, we confirmed that both study drugs have favorable safety profiles in this critically ill population.

A large, multicenter pediatric RCT will be needed to determine the effectiveness of t-PA dwells in reducing the risk of CADVT. Based on a risk of CADVT of 31.6%, 20% relative risk reduction of CADVT, type 1 error of 0.05 and power of 0.8, we will need 800 children per arm to complete this RCT. Patient factors including non-CVC risks for VTE (age, diagnosis, mechanical ventilation, inotropes use) and CVC factors (type, diameter, duration) may convey additive risk and need to be incorporated in the trial design.

**Conclusion**

Critically ill children requiring CVC are at high risk for CADVT. A future multicenter, blinded, RCT that will determine the effectiveness of t-PA vs UFH dwell in reducing CADVT is feasible, with favorable consent rates of approached patients and good adherence to study protocol.

**Abbreviations**

- CABSI-Catheter associated bloodstream infection
- CADVT-Catheter-associated deep venous thrombosis
- CVC-central venous catheter
- DVT- Deep vein thrombosis
- ICU- intensive care unit
- IQR-interquartile range
- RCT-Randomized controlled trial
- t-PA Tissue plasminogen activator
- UFH-unfractionated heparin
- VTE- Venous thromboembolism

**Declarations**
Ethics approval and consent to participate: This study was approved by Children's Hospital of Wisconsin Institutional Review Board (IRB# 1293254-5). Informed consent, and assent as appropriate, were obtained prior to starting any study procedures.

Consent for publication: not applicable

Data Availability: A de-identified version of the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests: The authors declare they have no competing interests.

Funding/Support: This study was supported by internal funding from the Department of Pediatrics, Medical College of Wisconsin

Author Contributions:

SJH was responsible for study conception and design, analysis and data interpretation, drafting and critical revision and final approval of manuscript. SS contributed to study design, data acquisition and interpretation, critical revision and final approval of the manuscript. EVSF contributed to study design, analysis and data interpretation, critical revision and final approval of the manuscript.

Acknowledgements: none

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Figures
Figure 1

Study Eligibility, Consent, Randomization and Completion Rates

Supplementary Files

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- CONSORTPilotTrialsChecklist8.25.21.doc