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

Sheila J Hanson (shanson@mcw.edu)
Medical College of Wisconsin https://orcid.org/0000-0001-6946-4549
Sadaf Shad
Medical College of Wisconsin
E. Vincent S. Faustino
Yale-New Haven Children's Hospital

Research Article

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

Posted Date: September 3rd, 2021

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

Abstract

Backround: 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 One child was withdrawn immediately after randomization due to development of exclusion criterion.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.[3–5] 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.[7–9] For prophylaxis, t-PA infused to dwell in dialysis catheters is associated with lower risk of CADVT than unfractionated heparin (UFH) dwell.[10–13] 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 ≤ 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, CABSI 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.[15] 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

	Patients N = 20
Patient factors	
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
Lowe 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.[15] Six of 19 children (31.6%) developed CADVT, 1 of which was occlusive. There were no episodes of CABSI. 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 wasapproved 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

References

1. Solutions for Patient Safety [updated. 2017; cited 2017 February 12]. Available from: .
2. Goudie A, Dynan L, Brady PW, Fieldston E, Brilli RJ, Walsh KE. Costs of venous thromboembolism, catheter-associated urinary tract infection, and pressure ulcer. Pediatrics. 2015;136(3):432–9. doi:10.1542/peds.2015-1386. PubMed PMID: 26260712. Epub 2015/08/12.
3. Mahajerin A, Branchford BR, Amankwah EK, Raffini L, Chalmers E, van Ommen CH, Goldenberg NA. Hospital-associated venous thromboembolism in pediatrics: A systematic review and meta-analysis of risk factors and risk assessment models. Haematologica. 2015;100(8):1045–50. PMID:26001789.
4. Raffini L, Trimarchi T, Beliveau J, Davis D. Thromboprophylaxis in a pediatric hospital: A patient-safety and quality-improvement initiative. Pediatrics. 2011;127(5):e1326–32. PMID:21464186.
5. Monagle P, Adams M, Mahoney M, Ali K, Barnard D, Bernstein M, Brisson L, David M, Desai S, Scully MF, Halton J, Israels S, Jardine L, Leaker M, McCusker P, Silva M, Wu J, Anderson R, Andrew M, Massicotte MP. Outcome of pediatric thromboembolic disease: A report from the Canadian Childhood Thrombophilia Registry. Pediatr Res. 2000;47(6):763–6. PMID:10832734.
6. Thakarar K, Collins M, Kwong L, Sulis C, Korn C, Bhadelia N. The role of tissue plasminogen activator use and systemic hypercoagulability in central line-associated bloodstream infections. Am J Infect Control. 2014;42(4):417–20. PMID:24559598.

7. Deitcher SR, Fesen MR, Kiproff PM, et al. for the Cardiovascular Thrombolytic to Open Occluded Lines-2 Investigators. Safety and efficacy of alteplase for restoring function in occluded central venous catheters: results of the Cardiovascular Thrombolytic to Open Occluded Lines trial. J Clin Oncol. 2002;20(1):317–24.
8. Ponec D, Irwin D, Haire WD, et al. Recombinant tissue plasminogen activator (alteplase) for restoration of flow in occluded central venous access devices: A double-blind placebo-controlled trial—the cardiovascular thrombolytic to open occluded lines (COOL) efficacy trial. JVIR. 2001;12:915–55.
9. Blaney M, Shen V, Kerner JA, et al. Alteplase for the treatment of central venous catheter occlusion in children: results of a prospective, open-label, single-arm study (The Cathflo Activase Pediatric Study). J Vasc Interv Radiol. 2006;17:1745–51.
10. Firwana BM, Hasan R, Ferwana M, et al. tissue Plasminogen activator versus heparin for locking dialysis catheters; A systematic review. Avicenna J Med. 2011;1(2):29–34.
11. Schenk P, Rosenkranz AR, Woflfl G, et al. Recombinant tissue plasminogen activator is a usefu alternative to heparin in priming quinton permacath. Am J Kidney Dis. 2000;35:130–6.
12. Gittins NS, Hunter-Blair YL, Matthews JN, et al. Comparison of alteplase and heparin in maintain the patency of paediatric central venous haemodialysis lines: A randomized controlled trial. Arch Dis Child. 2007;92:499–501.
13. Hemmelgarn BR, Moist LM, Lok CE, et al. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. N Engl J Med. 2011;364:303–12.
14. Malec LM, Cooper J, Rudolph J, Michaels MG, Ragni MV. Prophylactic rtPA in the prevention of line-associated thrombosis and infection in short bowel syndrome. J Pediatr Gastroenterol Nutr 2017.
15. Arnold DM, Burns KE, Adhikari NK, Kho ME, Meade MO, Cook DJ, McMaster Critical Care Interest Group. The design and interpretation of pilot trials in clinical research in critical care. Crit Care Med. 2009 Jan;37(1 Suppl):69–74.

Figures

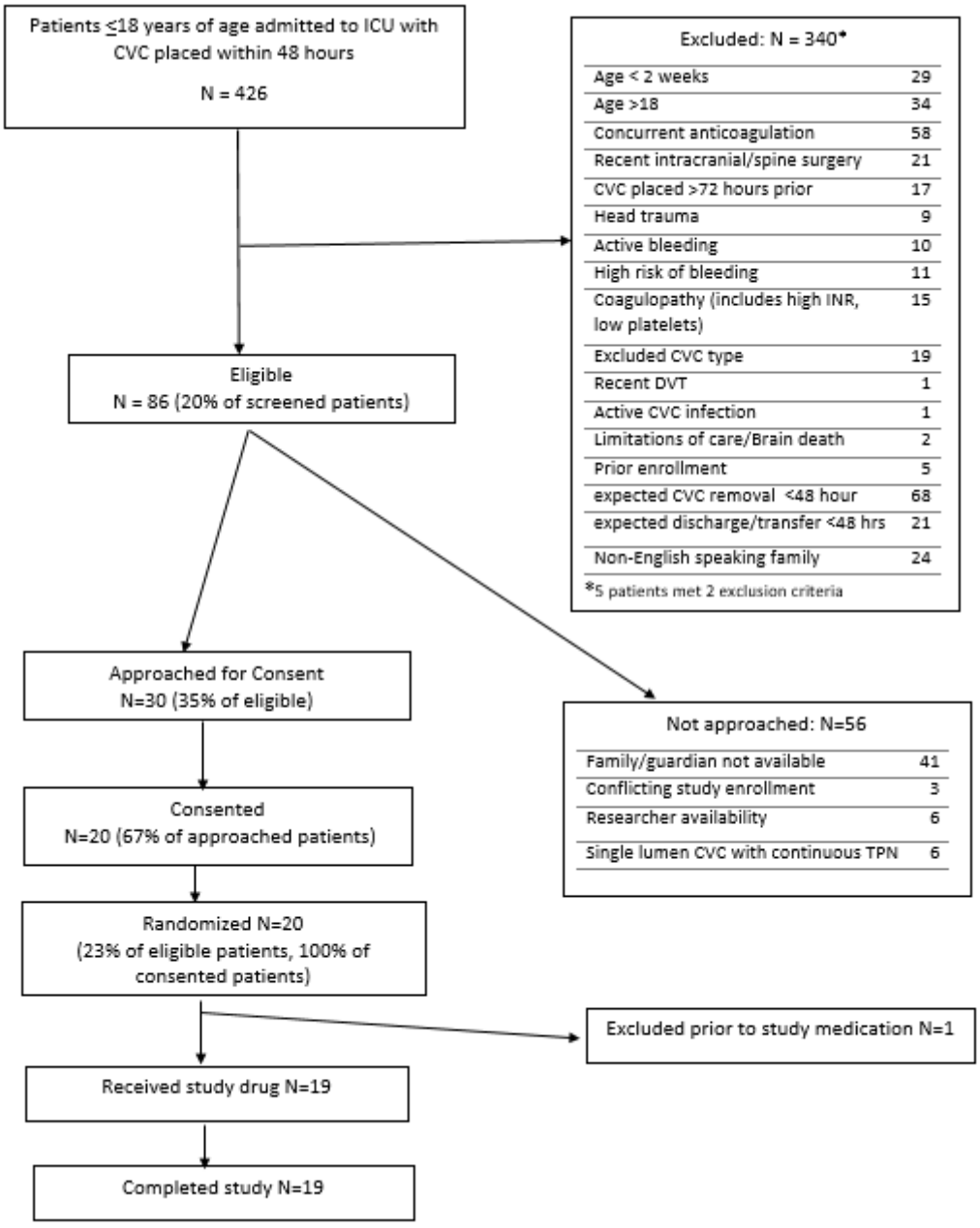

Figure 1

Study Eligibility, Consent, Randomization and Completion Rates

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORTPilotTrialsChecklist8.25.21.doc