A review of clinical characteristics and outcomes of combined thrombolysis and anticoagulation for pediatric lower extremity and inferior vena cava thrombosis

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Abstract

Objective: Effective treatment for acute limb-threatening lower extremity (LE) thrombosis involves thrombolysis in addition to anticoagulation. There is limited available data on the outcomes and safety of catheter directed thrombolysis (CDT) to help guide its use in pediatrics. Procedure: Single-center retrospective medical record review of children (<21 years of age) that received CDT for LE and inferior vena cava (IVC) thrombosis over a 5-year span at a pediatric tertiary care center. Results: A total of 29 patients were identified for inclusion in the study, 76% (n=22) received overnight CDT while 24% (n=7) received tissue plasminogen activator (tPA) as a bolus dose during a single interventional procedure. The median age of the cohort was 15.8 years (range 0-19.1). All patients were treated with a course of anticoagulation. The thromboses represented were extensive, with 93% (n=27) being occlusive and affecting multiple venous segments. Thrombus resolution occurred in 35% (n=10) of patients. Rivaroxaban use during the course of anticoagulation and estrogen-containing hormonal therapy use prior to diagnosis were associated with thrombus resolution, while Hispanic ethnicity was associated with thrombus persistence. There was one major and 3 minor bleeding events that occurred as a complication of thrombolysis and no treatment related deaths. Conclusions: The administration of tPA, whether by CDT or as an intra-procedural bolus, for extensive LE and IVC thromboses is effective and safe in children when combined with a course of anticoagulation.

Introduction

The standard recommendation for the majority of pediatric venous thromboses is anticoagulation alone. However, for life, limb, or organ-threatening thromboses site directed tissue plasminogen activator (tPA) is recommended to rapidly restore blood flow and perfusion to the affected anatomical regions.[1,2] Inadequate treatment of deep venous thrombus (DVT) in pediatric patients may result in a lifetime of disability and reduced quality of life secondary to post-thrombotic syndrome (PTS), characterized by chronic leg swelling, pain, and venous insufficiency.[3-7] As pediatric tertiary care centers are seeing an increase in the diagnosis of venous thromboembolism (VTE) in hospitalized patients,[8] it is necessary to understand the outcomes and adverse events of the current treatment modalities that are available for children. This is especially important now due to the increased risk of thrombosis seen in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.[9-11]

Catheter-directed thrombolysis (CDT) is one treatment modality used in pediatric tertiary care centers by interventional radiologists (IRs) and involves placement of a specialized infusion catheter at the site of thrombosis to infuse tPA. Additional interventional measures include mechanical thrombectomy devices to mechanically remove thrombus burden with (pharmacomechanical thrombectomy) or without (mechanical thrombectomy) tPA at the time of the procedure. Large prospective studies evaluating the long-term effects

and safety of CDT have been performed in the adult population.[12-14] While the safety and effectiveness of endovascular thrombolysis for acute DVT has been demonstrated in children,[15-18] there is limited available data on the risks and long-term thrombosis outcomes in pediatric patients who undergo CDT. Moreover, there is a lack of data describing different methods of tPA administration (tPA administered via CDT for an extended period of time or bolus "on-table" dosing of tPA administered during a singular interventional procedure), as well as different mechanical thrombectomy devices (including the AngioJet Thrombectomy™ and Penumbra Indigo® Systems) in the pediatric population.

We performed a single-center retrospective review of children at our pediatric tertiary care center who received CDT for lower extremity (LE) venous and/or or inferior vena cava (IVC) thrombosis to develop a comprehensive understanding of our multi-disciplinary treatment approach to, and outcomes in this patient population. Our outcomes focused on thrombosis resolution and safety (bleeding events) of pediatric thrombolysis, evaluating different methods of thrombolysis and interventional approaches.

Methods

Study design

A retrospective chart review was performed on pediatric patients (under 21 years of age) with LE or IVC thrombosis that were treated with thrombolysis therapy and anticoagulation at Texas Children's Hospital. Patients were evaluated within the time period 2015 and March 2020 (time of data collection). The study was approved by the institutional review board.

Study objective

This study was undertaken to characterize the outcomes and complications of thrombolytic therapy for pediatric thrombosis at our tertiary care center. We also sought to compare patient outcomes when different interventional approaches were used: CDT via an indwelling venous catheter versus bolus tPA administration "on-table" during a single interventional procedure without subsequent catheter-directed tPA infusion. Thrombolysis refers to the active administration of a thrombolytic agent (in this case, tPA). Catheter-directed thrombolysis involves the distribution of tPA through a multi-side hole infusion catheter to allow systemic distribution of the agent at a controlled rate over a length of time. Therefore, a patient who undergoes on-table thrombolysis prior or after the initiation of CDT receives tPA. On-table tPA is a bolus dose that is made into the area of thrombus and then followed by other various intervention. The patients in this review did not undergo post-procedural CDT.

Patient selection

The electronic medical record system at our institution was queried for patients who met inclusion criteria for our study: pediatric patients (under the age of 21 years) who received interventional thrombolytic therapy for a symptomatic venous thrombosis of the LE and/or IVC. Patients that received thrombolysis for additional reasons (line dysfunction, upper extremity) were excluded in medical record query or analysis.

Variables evaluated

Data collected included patient demographics, risk factors for DVT development, characteristics of the thrombus, anticoagulation used, and interventional therapies utilized. Risk factors for DVT included inherited and acquired thrombophilias (prothrombin G20210A and Factor V Leiden mutations, decreased protein C, S, and antithrombin, elevated lipoprotein [a], homocysteine, and antiphospholipid antibodies), hospital-related (presence or history of central venous catheters, recent immobilization, surgery, or trauma), disease-related (infection, cancer, inflammatory bowel disease, or nephrotic syndrome), or medication-related (estrogen, steroids, or asparaginase). Characteristics of the thrombus included laterality, veins involved, extent of thrombus, and presence of pulmonary embolus (PE). Interventional therapies included use of CDT, Angiojet for thrombectomy and pharmacomechanical thrombectomy, Indigo system for mechanical thrombectomy, stent placement, intravenous ultrasound [IVUS], and percutaneous transluminal angioplasty [PTA].

Outcomes

The main patient outcomes that were evaluated were efficacy of therapy (measured by complete thrombus resolution following diagnostic intervention and a course of anticoagulation), and safety (measured by bleeding events following the procedure). For patients who had serial follow up images available for review, the 6-month follow up image (or closest available to 6 months after diagnosis) was the time point selected. If follow up imaging was not performed at 6 months or later, the latest follow up image prior to the 6-month point was used. Severity of bleeding was classified according to the International Society of Thrombosis and Haemostasis (ISTH) scale, with major bleeding episodes defined as fatal bleeding, bleeding with a decrease in hemoglobin of 2 g/dL in a 24-hour period, retroperitoneal bleeding, intracerebral bleeding, or bleeding that requires surgical intervention in operating rooms. Non major bleeding events include documented bleeding that did not meet criteria for a major bleeding episode (referred to as clinically relevant non-major and minor bleeding in the ISTH scale).[19] As many of the interventional technologies employed are red blood cell depletive without leading to actual bleeding, post-interventional declines in hemoglobin that were noted without an identified bleeding event were not counted as bleeding adverse events.

The major outcomes were evaluated within the two thrombolysis groups; CDT and "on-table" thrombolysis. Additional secondary outcomes included thrombus progression/recurrence and PTS. At the time of evaluation, our center did not incorporate standard PTS scoring systems into our follow up records; nonetheless, standard symptoms of PTS were recorded, including extremity swelling, pain, redness, fullness, decreased range of motion, heaviness, and presence of ulcers. Review of symptoms for PTS were delayed until the acute phase of the DVT has passed, at 6 months following diagnosis.[20]

Statistical analysis

Patient data was collected, de-identified, and stored in an online database (Redcap, Vanderbilt University; Excel Microsoft Corp.). All non-categorical data were evaluated for normality. Descriptive statistics included mean/SD, median (range) and N (%) based on normal, non-normal and categorical data type respectively. We compared patients who had resolution at 6 months with those who did not by t-test for normally distributed data, Wilcoxon rank sum test for non-normal data and chi-square test/exact test for categorical data. $P<0.05$ was considered significant. All analyses were performed in SAS Statistical Software (version 9.4, Cary, NC).

Results

Patient cohort

Our medical record query resulted in 32 total patients. Of those patients, 3 were excluded from analysis as they involved upper extremity thromboses. The remaining 29 patients had thromboses that involved veins of the LEs and/or IVC. Of the 29 patients that met inclusion criteria, 22 received overnight catheter-directed tPA via an indwelling venous catheter and 7 received "on-table" tPA as bolus dosing during the interventional procedure without additional CDT or tPA following completion of the procedure. Patient demographics and characteristics are listed in **Table 1** .

Thrombus characteristics

Thromboses evaluated were in the LEs in 93.1% (n=27) and IVC in 13.8% (n=4); 48.1% (n=13) were left sided, 44.4% (n=12) were right sided, and 13.8% (n=4) were bilateral. Multi-level thrombosis (involving more than one of the following venous segments: IVC, iliac, femoral, or popliteal) was present in 93.1% (n=27) of patients. Upon diagnosis the thrombosis was noted to be occlusive in 93.1% (n=27) and non-occlusive in 6.9% (n=2). Pulmonary embolism (PE) was present in 27.6% (n=8) on initial presentation. The most common symptoms at presentation included swelling (86.2%, n=25), pain (72.4%, n=21), and redness (20.7%, n=6) of the affected lower extremity. The median number of days patients were experiencing symptoms prior to DVT diagnosis was 4, with a range of 0 to 40 days. A total of 4 patients (13.8%) were diagnosed with their DVT after experiencing symptoms for over 14 days, suggestive of subacute thrombosis, but still underwent subsequent interventional therapy.

Treatment characteristics

All patients in the cohort received anticoagulation, see **Table 2** for details. In the "on-table" bolus group (n=7), the median tPA dose was 7 mg (range 2-10 mg), and median tPA dose/kg was 0.2 mg/kg (range 0.2-0.3 mg/kg). The median dose/kg/hr of tPA received in the indwelling catheter group was 0.02 mg, with a range of 0.01-0.045 mg. The number of days that tPA was infused in the catheter-directed group was 1 in 59.1% (n=13), 2 in 13.6% (n=3), 3 in 18.2% (n=4), and 4 days in 9.1% (n=2). See **Table 2** for types of pharmacomechanical devices used.

Thrombus resolution

The main outcome evaluated in our patient cohort was complete thrombus resolution (without residual thrombosis) following treatment. Follow up imaging performed at 6 months (for those patients who did not have repeat imaging performed at 6 months, the most recent image prior to 6 months was collected) revealed complete thrombus resolution in 34.5% (n=10) of patients. Of the 19 patients that did not have complete resolution, 47.4% (n=9) had residual complete occlusion and 52.6% (n=10) had residual partial occlusion noted. The last dedicated venous imaging performed was under 6 months in 62.1% (n=18) of the cases. In patients who had serial imaging beyond 6 months, no change in the thrombus burden was noted when compared to earlier time points. The range of final follow up images available was 0.5 to 15 months (median 4 months). There were three patients that transferred care to another institution (due to closer proximity to their homes) whose last available follow up image was less than 2 months following DVT diagnosis and intervention with residual thrombosis present. Doppler ultrasonography was the imaging modality for 96.6% (n=28) of final follow up images; one patient had venography as the modality of final follow up image. Overall, non-Hispanic patients (60% white, 20% each African American or Asian) had a trend for higher rate of thrombus resolution (45.5%, n=10) compared to those of Hispanic ethnicity (all white) who had no cases of thrombus resolution (p=0.06).

Patients that received bolus tPA "on-table" alone had resolution in 57.1% (n=4) while those that received CDT had resolution in 27.3% (n=6, p=0.19 fisher exact test).

Patients that received thrombolysis via Angiojet had a higher rate of thrombus resolution compared to those that did not receive Angiojet thrombolysis, 62.5% vs 23.8%, respectively, although this difference did not reach statistical significance in our sample (p=0.08). There was no difference in thrombus resolution noted when comparing those patients who underwent intravascular stent placement and those who did not.

Patients that received rivaroxaban as an anticoagulant had a higher rate of thrombus resolution compared to those who did not, 75% vs 19% (OR=12.75, 95% CI=2.10-114.33; p = 0.009). This relation remained significant after control for potential confounding influence of ethnicity (adjusted OR=7.5; 95% CI=1.17-69.21; p=0.045). Other anticoagulants used (unfractionated heparin [UFH], low molecular weight heparin [LMWH], warfarin, and bivalirudin) were not associated with thrombus resolution.

Furthermore, the risk factor of hormonal therapy use was associated with thrombus resolution, as those taking estrogen-containing hormonal therapy prior to diagnosis experienced thrombus resolution in 83.3% (n=5) of cases, while those not on hormonal therapy had thrombus resolution 21.7% (n=5) of the time (p=0.01). No other risk factor studied was associated with thrombus resolution (see **Table 3**).

Adverse events

Thrombus progression or recurrence occurred in 34.5% (n=10) of patients; 40.9% (n=9) in those that received CDT and 14.3% (n=1) in those that received "on-table" tPA. The median time to thrombus progression or recurrence was 0.5 months (range 0.1-14 months) noted on follow up imaging. Minor bleeding complications were noted in 10.3% (n=3) of patients with 3.4% (n=1) experiencing a major bleeding episode following their interventional procedure. The minor bleeding events were minor oozing from venous access sites, epistaxis, and the development of a large (8.2 cm) popliteal hematoma that did not require intervention beyond temporary cessation of anticoagulation and tPA. The major bleeding episode occurred in a neonate who had a large drop in hemoglobin (decrease of 9.9 g/dL) requiring multiple transfusions. While there was no bleeding source identified, this was counted as a major bleeding event due to the large drop in hemoglobin

requiring multiple blood transfusions. Three of the bleeding events (including the major bleed) occurred in the patients in the CDT group, with a frequency of 13.6%; one minor bleeding episode occurred in the patients that received "on-table" tPA, a frequency of 14.3%. The median drop in hemoglobin following the procedure was 2.3 g/dL from the pre-procedural blood count; 24.1% of patients (n=7) required a blood transfusion for an acute decline in hemoglobin following the procedure. As the use of interventional devices may result in a decline in measured hemoglobin due to intra-procedural red blood cell depletion (e.g. Indigo thrombectomy, Angiojet thrombolysis and thrombectomy), post-procedural drops in hemoglobin were not counted as bleeding events unless a bleeding event was noted via physical examination or imaging. The median decline in platelet count was 50,000 cells/dL from pre-procedural labs. There were no noted cases of PE following a thrombolysis procedure.

Though our center did not use standardized PTS scoring scales in follow up appointments, 17.2% (n=5) of patients exhibited symptoms of PTS at follow up hematology outpatient visits. This represents 18.2% (n=4) of the CDT and 14.3% (n=1) of the "on-table" groups. These symptoms included lower extremity pain (10.3%, n=3), swelling (10.3%, n=3), and redness/discoloration (3.4%, n=1). The median time from diagnosis/intervention to the development of PTS symptoms was 15.3 months, with a range of 7 to 22.3 months. One patient in the cohort died, though was unrelated to thrombolysis or anticoagulation (died of complications of sepsis without bleeding symptoms noted; he was on anticoagulation for continued therapy of his thrombosis during the hospitalization).

Discussion

Our experience in children demonstrates that CDT, in combination with systemic anticoagulation, is a safe and effective treatment modality for life- or limb-threatening thrombosis. Of the 29 patients that were included in the analysis there was only one major[19]and three non-major bleeding events that were described. The major bleed involved a precipitous drop in the hemoglobin of a neonate following the interventional procedure that required multiple blood transfusions, while the minor bleeds only required temporary cessation of CDT and anticoagulation to resolve. This review also provides descriptive information that may help pediatric hematologists and IRs prepare the post-procedural expectations of staff and patients, including post-procedural decline in hemoglobin (2.3 g/dL), and platelets (50,000 cells/dL), with ˜25% of patients requiring a transfusion after the procedure.

The rate of complete thrombus resolution of 34.5% in our patient cohort compares favorably to other studies evaluating outcomes of LE DVT in children. Specifically, the findings by Avila et al. noted a complete resolution rate between 19.6 and 30.9% in neonates and non-neonates at the end of therapy images.[21] Our thrombosis resolution rate is notable due to the extent of thromboses that were included in our study, with 93% having multiple segments of occlusion, and those patients who are selected for thrombolysis at our institution have increased vascular compromise, secondary to extensive thrombosis, compared to those treated with anticoagulation alone. Our findings also add to the evidence that Hispanic patients affected with vascular disease have worse outcomes (in our case, thrombus resolution) than those patients that identify as non-Hispanic,[22-24]with no Hispanic identifying patients experiencing thrombus resolution compared to 45.5% of non-Hispanic patients. This may suggest the need for more aggressive interventional and medical approaches in Hispanic children with LE or IVC DVT.

Patients that received the anticoagulant rivaroxaban during their treatment course had a 6-fold increase in the rate of thrombus resolution, which remained significant after controlling for ethnicity. The direct oral anticoagulant rivaroxaban is becoming increasingly used for VTE in children,[25] with the advantages of not requiring laboratory monitoring and the ease of oral administration. While we cannot conclude on reasons for the enhanced efficacy of this drug, it may be secondary to better compliance over other agents in our population. Our data suggests that the medication should be considered for anticoagulation in children affected with extensive LE and IVC thrombosis, especially in the adolescent age range due to ease of dosing regimen. It is important to note, however, that rivaroxaban is not currently approved by the FDA for use in children. The risk factor of estrogen-containing oral hormonal therapy (a reversable thrombosis risk factor upon cessation of the medication) was also associated with thrombus resolution.

In general, most devices used in pediatrics are considered "off-label," as they do not have specific pediatric approval. The use of Angiojet for patients less than 18 years of age has not received approval via the FDA, and studies are not available in the pediatric population. A thorough review of the literature does not suggest a detrimental safety profile for device use in the less than 18-year-old population, and multiple studies have documented use of the Angiojet in this population without significant incident.[26,27] It is important to note that patients can have temporary bradyarrhythmia as a result of the use of this device, regardless of which vascular territory it is being used in.[28]

Based on the analysis of our data, the use of Angiojet as part of interventional therapy during pediatric thrombolysis *trends* to improved resolution of the thrombus burden. While this might be a part of the impact of aggressive utilization of tPA, as this trend was also noted with relatively better thrombus clearance and less progression in our "on-table" tPA administration only cohort, the use of the thrombolytic function of the Angiojet with "lace and lyse" delivery of tPA may be a superior modality for interventional thrombolysis. The use of tPA in this cohort can assist with thrombus clearance and potentially avoid mandated ICU stays associated with CDT. Furthermore, these results will lead us to consider changing our practice to using the Angiojet device with "on-table" tPA when the circumstances permit.

In addition, as has been noted in multiple adult studies, the use of tPA for venous thrombolysis carries a relatively low risk profile in the pediatric population.[29-32] One does need to be careful in this population as pediatric patients process tPA differently than adults. It is known that neonates and young infants have lower plasminogen levels than older children and adults[33]which may lead to inadequate fibrinolysis unless plasminogen is supplemented.[34]

There is a valid concern with respect to intra-procedural blood loss with the use of thrombectomy or thrombolysis devices. All utilized devices carry some risk of direct or indirect blood loss with their utilization; e.g. the hemolytic side effect of the Angiojet and the potential for blood loss with other aspiration devices. We did note that our patients experienced decrease in their hemoglobin (>2g/dL) regardless of whether it required intervention.

Limitations of this study include its retrospective nature and limited sample size. As treatment decisions were not randomized but at the discrepancy of the treating physicians, it is difficult to make direct comparisons of treatment approaches between patients. This review does, however, provide a baseline understanding for this important and growing population and allows our institution and others the ability to develop systematic and uniform approaches to pediatric patients with extensive LE and IVC thrombosis. We will continue to evaluate outcomes and adverse events with pediatric thrombolysis moving forward, including the use of a dedicated outcomes survey.

In conclusion, the experience at our pediatric institution demonstrates that tPA administration, whether by CDT or as an intra-procedural bolus, in combination with anticoagulation is an effective and safe approach to extensive pediatric LE and IVC thrombosis. The improved thrombosis resolution rate with rivaroxaban needs additional future investigation, though is encouraging for pediatric patients requiring thrombolysis for acute thrombosis. Future prospective and multi-institutional studies are needed to develop a widely accepted and optimized approach to pediatric thrombolysis.

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Data sharing statement : The data that support the findings of this study are available from the corresponding author upon reasonable request.

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