



Published in final edited form as:

J Vasc Interv Radiol. 2011 February ; 22(2): 121–132. doi:10.1016/j.jvir.2010.10.013.

Percutaneous Mechanical and Pharmacomechanical Thrombolysis for Occlusive Deep Venous Thrombosis of the Proximal Limb in Adolescents:

Findings from an Institution-Based Prospective Inception Cohort Study of Pediatric
Venous Thromboembolism

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Abstract

PURPOSE—Young individuals with occlusive, proximal limb DVT who have acutely elevated plasma levels of factor VIII and D-dimer are at high risk for post-thrombotic syndrome (PTS) when treated with conventional anticoagulation alone. We sought to evaluate our experience with adjunctive percutaneous mechanical/pharmacomechanical thrombolysis (PMT/PPMT) in such patients.

PATIENTS AND METHODS—Among 95 children 11 to 21 years of age enrolled in a prospective cohort of venous thromboembolism between March 1, 2006 and November 1, 2009, 16 met eligibility criteria and underwent PMT/PPMT, typically with adjunctive catheter-directed thrombolytic infusion (CDTI) of tissue-type plasminogen activator given post-procedure.

RESULTS—Median age was 16 years (range: 11–19 years). Thirteen cases (81%) involved lower limbs. Underlying stenotic lesions were disclosed in 53%, with endovascular stents deployed in all cases of May-Thurner. There were no peri-procedural major bleeding events and one symptomatic pulmonary embolism. Technical success rate was 94%. Early (<30 days) locally recurrent DVT developed in 40%, of which 83% were successfully re-lysed. Late recurrent DVT rate (median follow-up duration: 14 months [range: 1–42 months]) was 27%. Cumulative incidence of physically and functionally significant PTS at 1–2 years was 13%.

CONCLUSION—This experience provides prospective evidence that PMT/PPMT with adjunctive CDTI can be used safely and effectively in adolescents with DVT at high risk for PTS.

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Conflicts of interest: None.

Introduction

Current consensus-based recommendations for antithrombotic therapy of deep venous thrombosis (DVT) in children suggest that thrombolytic interventions be reserved for patients with life- or limb-threatening events [1]. However, a risk of post-thrombotic syndrome (PTS) of nearly 80% was recently determined in a small cohort study evaluating a subgroup of young patients with DVT—defined by completely veno-occlusive proximal lower limb DVT in association with acutely elevated plasma levels of factor VIII and D-dimer—managed by conventional anticoagulation according to the present standard of care [2]. This study further observed that when thrombolysis (typically consisting of systemic tissue-type plasminogen activator [tPA] by low-dose continuous intravenous infusion, with salvage percutaneous mechanical or pharmacomechanical thrombolytic [PMT/PPMT] intervention for persistent occlusion) was employed prior to conventional anticoagulation, the risk of PTS was significantly reduced (OR=0.02, 95% confidence interval=<0.001–0.48), at 22%. This PTS rate is similar to the historical frequency of PTS recently defined in largely unselected children with a history of upper or lower extremity DVT by systematic review [3].

Present recommendations for antithrombotic management of DVT in adults suggest that thrombolysis be considered in young patients with a long anticipated lifespan who have a low bleeding risk and extensive and/or occlusive thrombus of recent symptomatic onset [4]. Since most children with PTS are anticipated to endure the associated symptoms and signs for a lifetime that spans many decades, it is imperative that risk-stratified antithrombotic therapeutic strategies be developed and prospectively studied in the pediatric population, with PTS risk reduction as a key aim. Principal among these strategies is the rapid restoration of venous patency via thrombolysis. To date, the few studies of thrombolysis in pediatric venous thromboembolism (VTE) have focused upon modalities of either systemic or catheter-directed thrombolytic infusion (CDTI), including tPA most recently and urokinase in the recent past [2,5,6]. However, a recent survey identified PMT/PPMT as the most commonly preferred approach to thrombolysis in pediatric DVT among physician members of the American Society of Pediatric Hematology/Oncology [7], even in the absence of any published experience apart from a few small retrospective case series. Accordingly, we sought to evaluate our institutional prospective cohort study experience with PMT/PPMT in adolescents with acute proximal limb DVT who were judged to be at high risk for PTS due to the combined presence of complete veno-occlusion and adverse prognostic biomarkers.

Methods

Subjects

Consecutive children evaluated for VTE at The Children's Hospital, Colorado and the Mountain States Regional Hemophilia and Thrombosis Center at the University of Colorado Denver were approached for enrollment in an institution-based prospective inception cohort study of pediatric VTE between March 1, 2006 and November 1, 2009 (Colorado Multiple Institutional Review Board approval #05–0339). Informed consent was provided in accordance with the Declaration of Helsinki. Study inclusion criteria for the present analysis consisted of: (1) Age ≥ 11 and ≤ 21 years at presentation; (2) symptomatic, completely veno-occlusive DVT of a proximal limb, objectively confirmed via appropriate radiologic imaging studies (compression ultrasound with Doppler, computed tomography with venography [CTV], magnetic resonance imaging with venography [MRV], conventional venography); (3) plasma factor VIII activity and D-dimer concentration above prognostic thresholds (150 U/dL and 0.5 $\mu\text{g/mL}$, respectively) upon initial testing within two weeks following DVT confirmation; (4) PMT/PPMT via an interventional radiologic approach; (5)

prospective follow-up in the Pediatric Thrombosis Program at the University of Colorado Denver and The Children's Hospital, Colorado; (6) signed informed consent/assent for study participation. The only exclusion beyond these eligibility criteria was a lag to PMT/PPMT of ≥ 60 days from time of symptom onset. Figure 1 provides a flow chart of study population eligibility.

PMT/PPMT regimens

Patients were carefully evaluated for contraindications to local thrombolysis (Figure 2); no children required exclusion for contraindications. In addition to informed research consent for cohort study participation, informed procedural consent was obtained in all cases. A clinical protocol was employed for each component of the PMT/PPMT intervention (Figure 3), which permitted variability in the number of modalities utilized, based upon clinical discretion. In brief, baseline venography was performed to establish anatomy, thrombus burden, and degree of occlusion. Using realtime ultrasound guidance, a 21-gauge needle was introduced into the popliteal vein for lower limb DVT or the basilic veins for upper limb DVT. In the setting of thrombus within one of these two venous systems, puncture was made peripheral to the thrombosed vein and an attempt at passing a wire through the thrombus was made. Via standard wire and catheter exchanges, a hydrophilic wire was advanced through the thrombus to its proximal (central) terminus and a central venogram was obtained. An appropriately-sized sheath was then placed over the guidewire.

One of three mechanical thrombectomy devices (AngioJet® [MEDRAD Interventional/Possis, Inc., Warrendale, PA, USA]; Amplatz ClotBuster® Thrombectomy Device [ev3 Inc., Plymouth, MN, USA]; or Trellis® [Bacchus Vascular, Inc., Santa Clara, CA, USA]), ranging in caliber from 5–8 F, was advanced through the sheath. Mechanical thrombectomy was performed according to manufacturer specification, in serial passes as necessary/possible to achieve maximal patency and minimal residual clot burden. When local tPA was administered via the device during MT (i.e.: Trellis®; some cases of ClotBuster® or Angiojet®), this was characterized as PMT. At the discretion of the operator (or in all cases of May-Thurner anomaly), additional percutaneous transluminal angioplasty was performed and one or more 12–16 mm stents (WALLSTENT®, Boston Scientific, Natick, MA, USA) were deployed at sites of residual stenosis. If thrombus was noted to extend peripheral to the popliteal vein (i.e. including calf veins), no attempt was made to lyse this portion of the thrombus. No duplicate venous systems were identified during this study.

In most cases, catheter-directed thrombolytic infusion (CDTI) was administered post-procedure directly into residual thrombus, for a period of 12–24 hours. CDTI uniformly employed tPA at 0.5–1 mg/hr via an infusion catheter placed in the sheath and directed at the site of PMT/PPMT or residual thrombus. During CDTI, unfractionated heparin was given at 10 U/kg/hr via the sheath (except in cases in which a diagnosis of severe thrombophilia [e.g., homozygous protein S deficiency] or thrombotic storm [8] was made, wherein more aggressive antithrombotic therapy was maintained [Table 3]).

Complete blood count, prothrombin time, activated partial thromboplastin time, fibrinogen activity (Clauss method), plasminogen activity, and D-dimer concentration were measured every 12 hours during, and for 24 hours after, the thrombolytic regimen. In the absence of bleeding concerns, therapeutic anticoagulation was transitioned to low molecular weight heparin (LMWH) 24-hours post-procedure, monitored by anti-Xa activity (goal: 0.5–1.0 anti-Xa U/mL). Anticoagulation was maintained with LMWH or warfarin (goal INR: 2.0–3.0) for a minimum total duration of six months, and not less than three months from the time of any stent placement. Duration of anticoagulation was guided by American College of Chest Physicians consensus-based recommendations [1].

Data collection

Systematic, prospective collection of clinically-derived data included: patient demographics; timing of symptom onset; thrombus site, extent and degree of occlusion; clinical risk factors for DVT; thrombophilia findings; presence of May-Thurner anomaly or Paget-Schroetter syndrome; interventions and medical regimens employed, and timing thereof; peri-procedural (≤ 7 days) major bleeding complications; peri-procedural pulmonary embolism (PE); technical success (end-of-intervention); rethrombosis (i.e., locally recurrent DVT); all recurrent VTE (all sites); and PTS. Major hemorrhage was defined as bleeding involving or resulting in any one of the following: central nervous system; retroperitoneum; decline in hemoglobin of ≥ 2 g/dL in a 24 hour period; need for invasive procedure to achieve hemostasis; death. In accordance with previously established reporting standards, technical success was characterized by grade II/III ($>50\%$) lysis, early locally recurrent DVT was defined as that which was objectively confirmed within 30 days post-intervention, and late recurrent DVT as greater than 30 days post-procedure [9].

Based upon institutionally-defined standard/best clinical care, all children underwent comprehensive thrombophilia testing as adapted from International Society of Thrombosis and Haemostasis recommendations [10] as previously described [11], in order to define risk factors for DVT onset and/or its recurrence. Severe deficiencies of coagulation regulatory proteins were defined as antithrombin <30 U/dL and protein C or protein S <20 U/dL), while mild deficiencies were defined as antithrombin 30–60 U/dL and protein C or S 20–40 U/dL. These deficiencies were further distinguished as inherited versus acquired based upon persistence versus non-persistence of the abnormality upon follow-up assessment 12 weeks or more from the time of initial testing, with supportive evidence provided via testing of family members.

Radiologic imaging surveillance was performed in order to exclude thrombus progression/recurrence on therapy as well as to define the extent of chronic thrombus burden of any residual thrombus. Specifically, imaging was repeated at end of PMT intervention, 1–4 weeks, 3–6 months, and (if persistent) at 1 year. Additionally, children were evaluated for PTS using the Manco-Johnson instrument at 3–6 months, 1 year, and annually thereafter in long-term follow-up. As reported previously [12], the Manco-Johnson instrument consists of a physical exam component (basic CEAP [13]) as well as a functional component (assessment of chronic pain with age-appropriate aerobic activities, activities of daily living, and at rest, using the Wong-Baker scale [14]). Validation data have been published for the use of the Manco-Johnson instrument in pediatric PTS assessment following DVT of the lower limbs [2], and have likewise been recently presented for non-catheter-related DVT of the upper limbs [15].

Statistical methods

Descriptive statistics were employed to define distributions of continuous data and frequencies/proportions of categorical data. Ninety-five percent confidence intervals (95% CI) were calculated using the Wald method. Cumulative incidence of PTS (expressed as a proportion) was calculated based upon findings at 1–2 years post-diagnosis; findings from the 2-year evaluation were used for this analysis, when available.

In the hypothesis tests, distributions and proportions were compared between groups of interest via Mann-Whitney U and chi-square testing, respectively, with Fisher's exact test used for circumstances in which frequency values were ≤ 5 in a 2-by-2 table. An alpha of 0.05 was considered statistically significant. All hypothesis tests were two-sided, and were performed using SAS 9.1 statistical software (SAS Institute, Cary, NC).

Results

Study population characteristics

Among 91 children aged 11–21 (inclusive) with VTE who enrolled in an institution-based prospective cohort study between March 1, 2006 and November 1, 2009, 19 had completely-occlusive proximal limb DVT in association with acute elevation of FVIII and D-dimer (Figure 1). Of these, 16 (18% of enrolled subjects with VTE) elected to undergo PMT/PPMT as part of clinical care within 60 days of symptom onset, after consideration of risks and benefits of treatment options. These 16 adolescents comprise the study population for the present analysis. Demographics, baseline patient and thrombus characteristics, and DVT risk factors in the study population are presented in Table 1.

Median age was 16 years (range: 11–19 years). Thirteen cases (81%) were lower limb DVT, nearly all of which involved the iliofemoral circulation. Four lower limb DVT cases (31%) involved the inferior vena cava (IVC). Underlying stenotic venous anomalies (specifically, May-Thurner anomaly or Paget-Schroetter syndrome) were definitively diagnosed in eight (53%) of 15 evaluable subjects (in subject #16, the thrombus was too organized to allow passage of a guidewire, and definitive diagnosis of Paget-Schroetter syndrome was therefore not possible due to subclavian involvement with residual occlusive thrombus). Endovascular stents were deployed in all cases of May-Thurner anomaly.

Treatment

Antithrombotic treatments, including thrombolytic interventions, are shown in Table 2. Five patients received low-dose systemic tPA (0.03–0.06 mg/kg/hr) by continuous intravenous infusion for 48–96 hrs prior to PMT/PPMT; in these cases, PMT/PPMT was initiated due to persistent veno-occlusion. PMT/PPMT was successfully conducted in 15 cases; CDTI was employed adjunctively in 11 (73%) of these. Retrievable IVC filters were placed in 6 subjects (38%). Median number of procedure days for PMT +/- CDTI was 2 (range: 1–4).

Outcomes

Safety and efficacy outcomes are summarized in Table 3. With regard to safety, there were no peri-procedural major bleeding events and one symptomatic pulmonary embolism. As for efficacy, technical success (grade II/III lysis) was achieved in 94% (95% confidence interval [CI]: 70–>99%) of cases. There were five acute local recurrences within one week (all of which were successfully re-lysed), one sub-acute, and four late local recurrences. Late local recurrences were restricted in all cases to patients with severe hypercoagulability, with or without underlying stenotic venous lesions, as follows: asparaginase-induced multiple thrombophilias (n=1); severe protein S deficiency with May-Thurner anomaly (n=1); antiphospholipid antibody syndrome (APS, n=1); and APS with May-Thurner anomaly (n=1). Using Society of Interventional Radiology outcomes reporting criteria [9; see also Methods], overall early (<30 days) and late (>30 days; median follow-up duration: 14 months [range: 1–42 months]) rethrombosis rates were therefore 40% (95% CI: 20–64%) and 27% (95% CI: 10–52%), respectively. Cumulative incidence of *any* PTS (physical findings on the basic CEAP component or chronic pain findings on the Wong-Baker component of the Manco-Johnson instrument) at 1–2 years was 80% (95% CI: 48–95%), while that of both *physically and functionally significant* PTS (abnormalities on both components of the instrument) was 13% (95% CI: 0.1–49%).

Prognostic factors for PTS

The results of univariate analyses for prognostic factors with regard to therapeutic efficacy are shown in Table 4. While no statistically significant associations were detected (and while sample size per group was small), a tendency toward increased risk of physically and

functionally significant PTS was observed among patients in whom: lag time from symptom onset to lytic intervention exceeded ten days; stenotic venous anomalies were disclosed (all of which were successfully stented); and PMT (rather than PPMT) was used. The latter observation was accompanied by a tendency toward increased rates of locally recurrent DVT for PMT in comparison to PPMT.

Discussion

The present findings provide prospective evidence that PMT/PPMT with/without adjunctive CDTI can be used safely in children, targeting a subgroup of adolescents with DVT known to be at high *a priori* risk for PTS. Peri-procedural symptomatic pulmonary embolism occurred in only one patient and major bleeding was absent among 16 consecutively enrolled cases in the cohort study. Despite acute locally recurrent DVT in 40%, 83% of these were successfully re-lysed. While late recurrent DVT occurred in 27% overall, all were in the setting of severe hypercoagulable states. Although signs and/or symptoms of PTS were still observed in some patients even when PMT/PPMT was performed within 10 days of symptom onset, the rate of functionally significant PTS occurred in only 13% of these high-risk patients. These findings identify PMT/PPMT with adjunctive CDTI as worthy of further prospective study as an effective and potentially safer (*vis-à-vis* systemic bleeding risk) alternative to systemic thrombolysis in children with occlusive proximal limb DVT who have adverse prognostic biomarkers at acute presentation.

Several additional observations in this study are important, including use of retrievable IVC filters and endovascular stents. Outcomes for the use of retrievable IVC filters in children have rarely been reported previously. The present finding of non-retrievability in two of six cases (33%) in which retrievable IVC filters were placed is consistent with a similar observation in one of six cases in the single prospective pediatric series of IVC filter use published to date [16]. In our series, non-retrievability was associated with accumulation of organized thrombus at the site where the filter legs apposed the IVC wall. In one case, there was a prolonged interval to filter retrieval (three months from time of placement). In the other, retrieval was within a conventional timeframe (six weeks from placement), but the patient's course was complicated by prolonged, severe coagulation activation as multimodal immunosuppressive and antithrombotic therapies were being escalated for the treatment of thrombotic storm in APS. These cases highlight the importance of careful consideration of risks and benefits of retrievable IVC filters in children, and the need for collaborative studies to provide more extensive data on this issue in the context of a rare disease.

Our preliminary finding of a low risk of recurrent VTE following iliac vein stenting for May-Thurner anomaly in children without severe underlying thrombophilia is supported by the two prior series (both retrospective) in this area [17,18]. None of the patients ≤ 21 years of age in these reports suffered recurrent VTE, at median follow-up durations of 11 and 18 months. Like our study, these prior series involved PMT/PPMT with/without CDTI prior to stent placement. Our prospective series involved six cases of May-Thurner anomaly. Among the five adolescents with May-Thurner anomaly in whom PMT/PPMT was performed within six weeks of symptom onset, with a median follow-up duration of 10 months, locally recurrent DVT developed in two subjects, both with severe underlying thrombophilia. In another case, recurrent VTE consisted of a distant event (subclavian DVT at the site of peripherally-inserted central catheter) unrelated to May-Thurner anomaly. Taken together, these experiences suggest that, in a disorder for which risk of recurrent VTE historically appears to be high, interventional thrombolysis with iliac vein stent placement may provide an effective means of secondary VTE prevention. However, our sample size with May-Thurner anomaly is small; as with the case of retrievable IVC filters, larger efforts are needed to adequately investigate this issue.

A recent systematic review of the literature revealed a weighted mean frequency of PTS in children of nearly 25%, albeit with considerable variability across eligible studies [3]. Pediatric findings with the use of a standardized PTS scoring system (adapted from Villalta scale) were first published in 2003 in a retrospective analysis by the Childhood Thrombophilia Program at the Hospital for Sick Children [19]; this study reported a prevalence of PTS of 63%. Prospective evidence using a pediatric PTS outcome measure, the Manco-Johnson instrument (for which validation data were subsequently published [2]), has indicated a cumulative incidence of PTS (as defined by physical or functional findings) of 33% at 1–2 years among unselected children [11]. In addition, a cumulative incidence of 77% was observed at approximately 2 years using the Manco-Johnson instrument in a small cohort of children with completely-occlusive lower limb DVT treated with standard anticoagulation in whom plasma levels of factor VIII and D-dimer were acutely elevated [2]. In this latter group, the frequency of PTS characterized by both physical and functional findings was 31%. The present finding of a cumulative incidence of physically and functionally significant PTS of only 13% at 1–2 years in a cohort of children sharing these adverse prognostic clinical and laboratory features indicates that PPMT deserves further evaluation as a potential means for PTS risk-reduction in this high-risk stratum of pediatric DVT.

The pathophysiology of PTS is thought to ultimately involve venous hypertension [20], which, in turn, is believed to derive from venous valvular reflux and/or persistent thrombotic veno-occlusion following DVT. The fact that PTS developed in several children in the present cohort in whom patency was both achieved acutely following PPMT and maintained long-term suggests that these patients may have irreversible valvular damage in the affected limb at the time of presentation or ongoing vascular inflammation following successful lysis. While plethysmography and other techniques of assessing venous valvular function were not performed in this cohort study, it should be recognized that PTS has been shown to correlate poorly with the presence of reflux by conventional methods [21]. As an alternative pathophysiological explanation to reflux secondary to mechanical valve damage, it is possible that valvular fibrosis and damage due to inflammation (whether systemic or localized to the vasculature) may be sufficient to cause insufficiency in these cases. Indeed, some evidence to date in adult DVT identifies elevated levels of interleukin-6 and D-dimer as prognostic of PTS [22,23]; the latter was a key inclusion criterion for cases in this cohort, based upon prior knowledge of prognostic factors for adverse outcomes of thrombosis in children [11].

Findings from a recent meta-analysis of randomized controlled trials (RCTs) of additional thrombolysis (systemic infusion or CDTI) versus standard anticoagulation alone revealed that, although mortality and the risk of recurrent VTE are not reduced by thrombolysis, the acute rate of complete patency is significantly increased (RR=4.14, 95% CI=1.22–14.01), and the risk of PTS is decreased (RR=0.66, 95% CI=0.47–0.94) [24]. However, a slight but statistically significant increase in acute major bleeding risk was ascribed to thrombolysis by systemic infusion/CDTI [RR=1.73, 95% CI=1.04–2.88]. Furthermore, the findings for PTS were based on only two RCTs in which this outcome was reported [25,26]. Recently (and not included in the aforementioned Cochrane review), early outcomes from the CaVenT trial indicate a significant risk reduction in chronic venous obstruction among adult patients with acute proximal DVT treated by additional CDTI when compared to those who received standard anticoagulation alone [27]. Evaluation for the primary endpoint of this trial, the rate of PTS at two years, is ongoing.

A potential advantage of the PMT/PPMT approach is the reduction in total dose of thrombolytic agent administered relative to thrombolysis by systemic infusion or CDTI, with a consequent theoretical benefit of decreased bleeding risk. Furthermore, PMT/PPMT

offers the advantage of minimizing *systemic* lytic exposure in particular, thereby presumably decreasing systemic bleeding risks involving critical sites such as the central nervous system. No RCTs of PMT/PPMT have been published, and prospective data on this lytic intervention for DVT are limited to two adult studies focused upon CDTI, in which PMT/PPMT was reported in a few cases each [28,29]. By comparison, nine retrospective studies have been reported, totaling approximately 200 adult DVT patients treated by PMT/PPMT with/without adjunctive CDTI [30–37]. However, published experience with a regimen of PMT/PPMT followed by adjunctive CDTI is limited to three retrospective studies in adults, in which the number of patients receiving this regimen ranged between eight and 20 [30,33,34].

With regard to safety of PMT/PPMT with/without CDTI, only six cases of acute major bleeding and zero cases of acute symptomatic PE were reported among the nine retrospective studies, out of 172 and 107 patients, respectively, in whom this outcome was assessed. These low rates of peri-procedural hemorrhage and PE are consistent with our prospective findings in the present cohort. As for potential efficacy of PMT/PPMT, acute patency rates were high across the nine retrospective studies. However, long-term patency was only reported by Lin and colleagues [31], who determined a rate of 65%. No cases of acute recurrent DVT were reported among a cumulative total of 62 subjects in the retrospective studies wherein this outcome was assessed. Our findings of a higher rate of early local recurrent VTE in this prospective cohort could be explained by one or more of the following possibilities: (1) the risk of acute re-occlusion may be higher in children than adults; (2) observation biases may have led to under-reporting in the retrospective studies; (3) children in the present study were generally more prothrombotic than the adults reported in prior series. Given the latter possibility, and the low bleeding risks observed here, the present authors currently advocate for more aggressive peri-procedural anticoagulation than employed in these subjects. With regard to PTS, the findings reported here are the first among prospective or retrospective studies of PMT/PPMT in children or adults. Future analyses of PMT/PPMT must build upon this work, emphasizing PTS as a key outcome, and using validated measures.

Principal strengths of the present work include: the prospective inception cohort design; comprehensive clinical and laboratory evaluation for predisposing conditions (including venous stenoses and thrombophilia states); standardization of peri-procedural and extended anti-coagulant regimens; and PTS outcomes measurement, using a standardized instrument for which data on validity have been published in children. The principal limitations of the present observational study are its non-randomized design and its relatively small size. As in other non-randomized studies, selection biases may exist (e.g., clinical determination of PMT vs. PPMT and use/non-use of CDTI). Additionally, in spite of the fact that this is the largest pediatric series on PMT/PPMT, and similar in size to previous adult studies of PMT/PPMT in which adjunctive CDTI was frequently employed, it must be emphasized that our outcome estimates (e.g.: acute locally recurrent DVT, PE, and major hemorrhage; late recurrent VTE; PTS) may be imprecise given the size of our study population. In particular, PTS may develop over time, and may be underestimated here; yet, in prior work by the authors, for all children found to be affected at 2 years, PTS had been evident at 1 year post-event [2]. Given the study limitations of sample size, the tendencies observed for putative prognostic indicators of long-term patency and PTS must also be considered speculative. Therefore, larger prospective studies are required in order to confirm the safety of PMT/PPMT with adjunctive CDTI, evaluate its efficacy for PTS risk reduction, and define additional prognostic factors in this young patient population.

Acknowledgments

N.A.G. conceived and designed the research, collected data, analyzed data, interpreted findings, drafted the manuscript, and approved its final submission. B.B., M.W., and C.R. collected data, analyzed data, interpreted findings, critically revised the manuscript, and approved its final submission. J.D.D. and M.J.M.-J. conceived and designed research, analyzed data, interpreted findings, critically revised the manuscript, and approved its final submission.

The authors thank Timothy Nelson and Elizabeth Pounder for assistance in data collection. This work would not have been possible without the generous participation of the patients/families in this observational study.

Grant support: Dr. Goldenberg is funded in part by a Career Development Award from the National Institutes of Health, National Heart Lung and Blood Institute (1K23HL084055). Dr. Manco-Johnson is supported in part by a Cooperative Agreement for a Pilot Thrombosis/Thrombophilia Network from the Centers for Disease Control and Prevention (U01DD00016).

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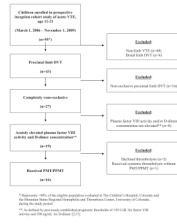


Figure 1. Flow chart of subject selection from the cohort study population, based upon clinical and laboratory characteristics of interest for heightened *a priori* risk of PTS.

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Figure 2. Observed relative contraindications to local thrombolytic intervention. These relative contraindications were adapted from absolute and relative contraindications to systemic thrombolysis. Contraindications were considered relative based upon the possibility of systemic exposure to thrombolytic agent in small amounts during PMT, or in large amounts during CDTI once patency achieved. No patients were excluded for contraindications.

Table 1

Demographics, baseline characteristics, and predisposing conditions of the study population.

Case #	Age (y)	Gender	DVT Site(s)	PE at presentation	Lag time from onset to dx (d)	Lag time from dx to thrombolytic rx (d)	Clinical triggers	Acute thrombophilia findings	Vascular anomaly	Other diagnoses
1	16	F	L iliac, fem, pop	No	1	45	Immobility	FVIII, LA, FVL het, PS (mild, acquired)	May-Thurner	Juvenile rheumatoid Arthritis
2	17	F	L iliac, fem, pop	No	3	0	OCP Trauma	FVIII, LA	May-Thurner	APS
3	16	M	R SC, ax, basilic	No	10	0	None	LA, beta-2-gp-1	Paget-Schroetter	APS
4	17	F	L iliac, Fem	No	7	26	OCP Trauma	n/a	May-Thurner	APS
5	16	F	IVC, R iliac, fem, pop	No	3	0	OCP EBV infection	FVL het FVIII	None	None
6	15	M	R iliac, fem	No	30	0	Obesity	FVL het FVIII	None	APS Trisomy 21
7	17	M	R SC	No	9	1	Chronic effort (baseball pitcher)	n/a	Paget-Schroetter	None
8	11	M	R iliac, L iliac, IVC	Yes	7	4	Trauma	FVIII, AT (mild, acquired), FVL het, LA, Lp(a)	May-Thurner	APS with thrombotic storm
9	15	M	L iliac, Fem	No	1	2	Trauma	LA, Beta-2-GPI, ACA	None	APS
10	17	F	R fem, pop, IVC	Yes	5	2	Obesity, OCP	FVIII, FVL het, LA	None	None
11	19	M	L fem, pop	No	6	8	ALL L-asp	AT (mild, acquired), PS (mild, acquired), FVIII	None	None

Case #	Age (y)	Gender	DVT Site(s)	PE at presentation	Lag time from sx onset to dx (d)	Lag time from dx to thrombolytic rx (d)	Clinical triggers	Acute thrombophilia findings	Vascular anomaly	Other diagnoses
12	17	F	L iliac, fem, pop	Yes	6	12	OCP	FVL het, PC (mild, inherited), FVIII	None	None
13	11	F	L fem	Yes	6	8	None	PS (sev, inherited) LA	May-Thurner	None
14	16	M	IVC, L iliac, B fem	No	4	6	None	LA, FVL/PT 20210 dual het	None	None
15	18	F	L iliac, Fem, pop	No	1	1	Immobility	FVIII, LA, FVL het, PS (mild, acquired)	May-Thurner	APS
16	14	M	L SC, ax	Yes	4	48	None	FVIII, LA, AT (mild, acquired), PC (mild, acquired)	n/a (obstructed by thrombus)	None

Abbreviations: DVT=deep venous thrombosis; PE=pulmonary embolism; dx= diagnosis; rx=treatment; F=female; M=male; fem=femoral; pop=popliteal; IVC=inferior vena cava; SC=subclavian; BC=brachiocephalic; ax=axillary; SVC=superior vena cava; L= left; R=right; B=bilateral; OCP=oral contraceptive pill (containing estrogen); FVIII=elevated factor VIII activity; LA=lupus anticoagulant; PS=protein S deficiency; sev=severe; FVL het=heterozygous factor V Leiden polymorphism; n/a=not available or not applicable; EBV=Epstein-Barr virus; ALL=acute lymphoblastic leukemia; L-asp: L-asparaginase; APS=antiphospholipid antibody syndrome

Table 2

Thrombolytic modalities, anticoagulant therapies, and additional therapeutic measures employed in the study population.

Case #	PMT/PPMT device*	PTA used during procedure	CDTI given post-procedure	Stent deployment (and site)	Retrievable IVC filter placement (and successful retrieval?)	Total # procedure days [†]	Post-lytic inter-ven-tion AC regimen [¶]	Extended AC Regimen	Dura-tion of AC (mo)
1	ClotBuster (PMT)	Yes	No	Iliac	Yes (no)	3	LMWH	LMWH x 6 mo, then warfarin	11+
2	ClotBuster (PMT)	Yes	Yes	Iliac	Yes (yes)	2	LMWH	Warfarin	22
3	AngioJet (PMT)	Yes	Yes	None	No	3 [§]	LMWH	Warfarin	12
4	AngioJet (PMT)	Yes	Yes	Iliac	No	2	LMWH	Warfarin	27+
5	AngioJet (PMT)	No	Yes	None	Yes (yes)	2	LMWH	Warfarin	3
6	AngioJet (PMT)	Yes	No	Iliac	Yes (yes)	1	LMWH	Warfarin	18+
7	AngioJet (PPMT)	Yes	No	None	No	1 [§]	LMWH	Warfarin	2+
8	ClotBuster (PPMT)	Yes	Yes	Iliac	Yes (no)	4	IV DTI	Fonda-parinux x 1 mo, then warfarin	17
9	ClotBuster (PPMT)	Yes	Yes	None	No	2	LMWH	Warfarin	26+
10	Trellis (PPMT)	Yes	Yes	None	Yes (yes)	2	LMWH	Warfarin	14
11	ClotBuster (PMT)	No	Yes	None	No	2	LMWH	LMWH	6
12	ClotBuster (PMT)	No	Yes	None	No	2	LMWH	Warfarin	3+
13	ClotBuster (PMT)	No	Yes	Iliac	No	3	LMWH	Warfarin	4+
14	ClotBuster (PPMT)	No	No	None	No	2	LMWH	Warfarin	3+

Case #	PMT/PPMT device*	PTA used during procedure	CDTI given post-procedure	Stent deployment (and site)	Retrievable IVC filter placement (and successful retrieval?)	Total # procedure days [†]	Post-lytic intervention AC regimen [¶]	Extended AC Regimen	Duration of AC (mo)
15	ClotBuster (PMT)	No	Yes	Iliac	No	2	IV DTI	Fondaparinux	1+
16	Failed (unable to insert guidewire into thrombus)	No	No	None	No	1	LMWH	Warfarin	2+

Abbreviations: AC=anticoagulant; tPA=tissue-type plasminogen activator; LD CIVI=; PMT=percutaneous mechanical thrombolysis (see Methods); PPMT=percutaneous pharmacomechanical thrombolysis (see Methods); CDTI: catheter-directed thrombolytic infusion (using tPA; see Methods); UFH: unfractionated heparin; LMWH: low molecular weight heparin; PTA=percutaneous transluminal balloon angioplasty; IV DTI=intravenous direct thrombin inhibitor

* Systemic tPA given by low-dose (0.03-0.06 mg/kg/hr) continuous intravenous infusion prior to PMT/PPMT in cases #1-3, 6.

[†] During initial hospitalization and within 10d post discharge

[¶] Immediate pre-procedural anticoagulation consisted of therapeutic UFH (goal anti-Xa activity = 0.3-0.7 U/mL) in all cases. UFH administration was suspended during PMT/PPMT procedure, except in cases #13 and 15, where UFH was maintained at subtherapeutic dosing of 10-12 U/kg/hr. UFH was maintained at 10 U/kg/h during CDTI, where employed.

[§] Does not include partial 1st rib resection, performed in both cases of Paget-Schroetter syndrome.

Table 3

Outcomes in the study population.*

Case #	Acute locally recurrent DVT within 7d of procedure, [†] and status on repeat procedure (re-lysed vs. refractory)	Follow-up duration at last clinic visit (mo)	Non-acute recurrent VTE, and type (local vs. distant)	Time from procedure to dx of non-acute recurrent VTE (mo)	Any PTS at 1-2 y	Physically and functionally significant PTS at 1-2 y	Basic CEAP findings	Wong-Baker chronic pain findings
1	None	12	Yes (distant)	4.5	Yes	n/a	C	n/a (pre-morbid chronic pain)
2	None	42	None	n/a	Yes	No	None	AA, ADL
3	Yes (re-lysed)	36	Yes (local)	0.5	Yes	No	None	AA
4	Yes (re-lysed)	27	Yes (local)	14	Yes	Yes	E	AA, ADL
5	None	30	None	n/a	Yes	No	None	AA
6	None	24	None	n/a	No	No	None	None
7	Yes (re-lysed)	2	None	n/a	n/a	n/a	n/a	n/a
8	Yes (re-lysed [§])	14	Yes (distant)	3-12 mo (asymptomatic)	No [¶]	No	None	None
9	None	26	Yes (local)	1-3 mo (asymptomatic)	Yes	No	E	None
10	None	14	None	n/a	Yes	No	E	None
11	None	18	Yes (local)	2 mo	Yes	No	None	AA, rest
12	None	6	None	n/a	n/a	n/a	n/a	n/a
13	None	10	Yes (local)	9 mo	n/a	n/a	n/a	n/a
14	None	3	None	n/a	n/a	n/a	n/a	n/a
15	Yes (re-lysed [§])	1	None	n/a	n/a	n/a	n/a	n/a

Case #	Acute locally recurrent DVT within 7d of procedure, [†] and status on repeat procedure (re-lysed vs. refractory)	Follow-up duration at last clinic visit (mo)	Non-acute recurrent VTE, and type (local vs. distant)	Time from procedure to dx of non-acute recurrent VTE (mo)	Any PTS at 1-2 y	Physically and functionally significant PTS at 1-2 y	Basic CEAP findings	Wong-Baker chronic pain findings
16	None	6	None	n/a	n/a	n/a	n/a	n/a

Abbreviations: DVT=deep venous thrombosis; PE=pulmonary embolism; PTS=post-thrombotic syndrome; CEAP= Basic Clinical-Etiologic-Anatomic-Pathophysiologic (American Venous Forum) physical exam component of the Manco-Johnson pediatric PTS instrument; W-B: Wong-Baker “faces” chronic pain

* There were no major bleeding events, and one symptomatic pulmonary embolism, within 7 days of procedure.

[†] Includes isolated stent thrombosis.

[‡] Reliability of assessment of basic CEAP component on contralateral difference in limb circumference may be limited due to bilaterality of DVT at presentation.

[§] Recurred twice in these subjects with multiple-antibody APS with thrombotic storm. Patency was eventually maintained post-MT/PMT in each patient only after multi-modal immunomodulatory therapy had been instituted and potent direct thrombin inhibition had resulted in marked decrease in D-dimer.

Table 4
Investigation of putative prognostic factors for development of PTS in the study population.*

	Lag time		Stenotic venous lesion [†]		APS		PPMT versus PMT [†]		Adjunctive CDTI [†]	
	≤ 10 d	> 10 d	Yes	No	Yes	No	PPMT	PMT	Yes	No
N (% of study population)	8 (50%)	8 (50%)	8 (53%)	7 (47%)	7 (44%)	9 (56%)	5 (37%)	10 (63%)	11 (73%)	4 (27%)
Median age (range) (y)	17 (15–18)	16 (11–19)	17 (11–18)	16 (14–19)	16 (11–18)	16 (11–19)	16 (11–17)	17 (11–19)	17 (11–19)	16 (15–17)
Gender (female n [group %])[‡]	4 (50%)	4 (50%)	5 (63%)	3 (43%)	3 (43%)	5 (56%)	1 (20%)	7 (70%)	7 (64%)	1 (25%)
Technical success (group %)[§]	100%	88%	100%	100%	100%	89%	100%	100%	100%	100%
Re thrombosis (group %)[§]	12%	12%	25%	0%	29%	11%	0%	20%	18%	0%
Any PTS (group %) [n evaluable]	80% [n=5]	50% [n=4]	80% [n=5]	50% [n=4]	50% [n=6]	100% [n=3]	33% [n=3]	83% [n=6]	71% [n=7]	50% [n=2]
Physically and functionally significant PTS (group %) [n evaluable]	0% [n=5]	33% [n=3]	25% [n=4]	0% [n=4]	17% [n=6]	0% [n=2]	0% [n=3]	20% [n=5]	14% [n=7]	0% [n=1]

Abbreviations: PTS=post-thrombotic syndrome; APS=antiphospholipid antibody syndrome; PMT=percutaneous mechanical thrombolysis; PPMT=percutaneous pharmacomechanical thrombolysis; CDTI=catheter-directed thrombolytic infusion (using tPA); n=number of patients.

* No statistically significant differences in intergroup distributions or proportions were detected. Note, however, that group same sizes were small.

[†] Subject #16 (in whom acute patency was not achieved) is not represented in the venous anomaly, PMT-versus-PPMT, or CDTI strata given that definitive diagnosis and lytic interventions were not feasible.

[‡] As defined by grade II/III lysis (see also Methods).

[§] Consists of early + late rethrombosis (see also Methods).