Tissue Plasminogen Activator Use in Children: Bleeding Complications and Thrombus Resolution

Deidra A. Ansah, MD[1], Kavita N. Patel, MD[1,2,3,4], Leticia Montegna, PharmD[4], George T. Nicholson, MD[1,4,5], Alexandra C. Ehrlich, MPH[5], and Christopher J. Petit, MD[1,4,5]

Objective To review our institutional experience with tissue plasminogen activator (tPA) to determine outcomes related to bleeding complications and thrombus resolution.

Study design We performed a retrospective review of all patients who received systemic tPA for thrombolysis. Data points included location of thrombus, initial and maximum tPA dose, and duration of tPA. The primary endpoint was bleeding complication.

Results Between 2005 and 2014, 46 patients received systemic tPA for thrombolysis: 17 (37%) were patients with a primary cardiac diagnosis, there were 17 (37%) hematology/oncology patients, and 12 (26%) patients with noncardiac, nonhematology/oncology diagnoses. The indication for tPA was central venous thrombus (n = 23), pulmonary artery thrombus (n = 9), and cardiac or aortic thrombus (n = 14). Bleeding complications occurred in 15 patients (33%). Median initial tPA dose in the bleeding complication group was 0.10 mg/kg/h vs 0.03 mg/kg/h in the group without bleeding complication group ($P = .01$). Cardiac patients experienced more bleeding complications ($P = .01$). Multivariate analysis indicated that dose of tPA ($P = .01$) and diagnostic category ($P < .01$) were associated with bleeding complication. Complete thrombus resolution occurred in 21 patients, partial in 10 patients, and no resolution in 15 patients. Complete resolution of thrombus was not associated with diagnosis, thrombus location, tPA dose, or duration.

Conclusions Cardiac patients appear to be at highest risk of bleeding complication; bleeding complications were associated with higher doses of tPA, and cardiac patients were the cohort who received the highest doses of tPA. Higher tPA doses are associated with increased risk of bleeding complication but are not associated with successful thrombus resolution. *(J Pediatr 2016;171:67-72)*.

See editorial, p 12

The occurrence of venous and arterial thrombosis in children is increasing while there is a paucity of literature on its effective management. The rising incidence of thrombosis in children has been reported as ranging from 18.8-58 per 10 000 hospital admissions.[1,2] The rising incidence is frequently attributed to advancements in treatment of critically ill children, including more use of indwelling catheters.[3] The greatest single risk factor in venous thrombosis is the presence of a central venous line. Children with congenital heart disease (CHD) are a high-risk group because of central venous lines as well as intravascular foreign materials including prosthetic valves, surgical shunts, and pacemaker leads.[4,5]

Primary management of thrombosis in children has focused on anticoagulants as initial therapy. Anticoagulants such as unfractionated heparin, low molecular weight heparin, and warfarin are commonly employed. The use of thrombolytic agents, specifically tissue plasminogen activator (tPA), is increasingly reported in children for indications such as life or limb threatening thrombi, massive pulmonary embolism, obstructive superior vena cava thrombus, cerebral sinus venous thrombosis, and shunt obstructions in children with complex CHD.[6,7] Studies have shown a decreased risk of postthrombotic syndrome with the use of tPA.[8] However, there is little published information on the efficacy, dose, and safety of tPA. Current recommendations for tPA dosing are based primarily on case studies and extrapolation from adult dosing.[9] Initial dose recommendations for children vary widely, with recommendations ranging from 0.01-0.6 mg/kg/h.[4,10] This wide range of recommended starting doses for tPA presents a challenge to the practitioner. We sought to review our institutional experience with tPA in patients with different primary diagnoses. Our specific goal was to assess efficacy of thrombolysis and bleeding risks across a range of tPA dosing.

CHD	Congenital heart disease
ICU	Intensive care unit
PICU	Pediatric ICU
tPA	Tissue plasminogen activator

From the [1]Department of Pediatrics, [2]Division of Pediatric Hematology, Oncology, and Bone Marrow Transplantation, Emory University School of Medicine; [3]Aflac Cancer and Blood Disorders Center; [4]Children's Healthcare of Atlanta; and [5]Sibley Heart Center Cardiology, Emory University School of Medicine, Atlanta, GA

The authors declare no conflicts of interest.

Portions of the study were presented during the meeting of the American Academy of Pediatrics, San Diego, CA, October 2014.

http://dx.doi.org/10.1016/j.jpeds.2015.11.020

Methods

This retrospective review included all children who received systemic tPA for thrombolysis from 2005-2014 at Children's Healthcare of Atlanta. We focused on tPA as it was the only thrombolytic therapy used at our institution. Patients were identified through our inpatient pharmacy database. Patients who received a single dose of tPA for central line clearance were excluded. The institutional review board approved this investigation.

Patient characteristics (age, weight, sex), primary diagnosis (characterized as primary [1] cardiac; [2] hematology/oncology; or [3] critical care for other pediatric patients without a primary cardiac, hematologic, or oncologic diagnosis) were noted. In addition, any surgical procedures up to 30 days prior to tPA administration were noted. The location of the thrombus was categorized as: (1) central venous including innominate vein, superior vena cava, and inferior vena cava; (2) pulmonary artery; and (3) cardiac/arterial including atrial, ventricular, aortic, and peripheral arterial thrombus.

Primary indication for tPA, the time interval from thrombus detection to tPA initiation, and the use of other anticoagulants and antiplatelet agents to resolve thrombus prior to tPA were recorded. The initial and maximum tPA doses as well as the total duration of tPA infusion were recorded for each patient. We do not have a standardized institutional protocol on tPA administration, therefore, dose and duration of tPA infusion was clinician driven. Available hematologic and coagulation laboratory values during tPA infusion were recorded. Administration of blood product transfusions (platelets, fresh frozen plasma, cryoprecipitate, packed red blood cells) during tPA administration was also noted.

The primary endpoint of the study was bleeding complication. All bleeding episodes documented during tPA administration were noted as a bleeding complication. Bleeding complications included both major (vital organ hemorrhage, central nervous system bleed, or any event requiring discontinuation of thrombolytic therapy) and minor (mucosal bleeding or bleeding from any peripheral or central venous skin insertion site). The secondary endpoint was thrombus resolution. Thrombus resolution was defined as none, partial, or complete based on follow-up ultrasound or angiographic imaging. Partial resolution was defined as an incomplete dissolution of thrombus and was specifically noted in the ultrasound or angiographic report.

A PubMed literature review using keyword search "tissue plasminogen activator use in children" was done to identify cohort studies with 5 or more patients investigating use of tPA in thrombolysis in the pediatric population.

Statistical Analyses

Data are presented as median (IQR) or n (%) where appropriate. Univariate analysis of factors associated with bleeding complications and thrombus resolution were evaluated using χ^2 chi-square or Fisher exact tests for categorical data and Student t test, Wilcoxon rank sum, or Kolmogorov-Smirnov test for continuous variables. Multivariable logistic regression was performed adjusting for relevant covariates. Receiver operator curves were created to assess risks of bleeding complication across a range of tPA doses. Analysis was performed using Statistical Analysis Software v 9.3 (SAS Institute, Cary, North Carolina). A P value of $<.05$ was considered statistically significant.

Results

Our cohort consisted of 46 patients (20 females) who received systemic tPA during the study period. The median age was 3.6 years (IQR 0.5-14.8), and the median weight was 14.8 kg (IQR 6.4-50.3) (**Table I**; available at www.jpeds.com). All patients were in intensive care units (ICUs) (cardiac ICU n = 17, pediatric ICU [PICU] n = 26, neonatal ICU n = 3) during tPA administration. There were 17 cardiac patients, 17 hematology/oncology patients, and 12 patients in the critical care category (**Table I**).

Of the 17 cardiac patients, 9 had single ventricle physiology. None of the cardiac patients developed a thrombus within 30 days of an interventional or diagnostic cardiac catheterization, however, 10 patients were within 30 days of a surgical procedure. Three cardiac patients had thrombi associated with prosthesis including 2 mitral valve replacements and a right ventricle to pulmonary artery conduit.

The hematology/oncology patients were predominately oncology patients (82%). Hematology diagnoses included hemoglobin SS and thrombophilia. The critical care category included patients with diverse primary diagnoses. Three of these patients were neonates. Location of thrombi included 23 (50%) central venous thrombi, 14 (30%) cardiac/arterial thrombi, and 9 (20%) pulmonary artery thrombi. Within the cardiac patient subgroup, there was a higher prevalence of cardiac/arterial thrombi (n = 10, 59%) ($P < .01$). The hematology/oncology patients were found to have more central venous thrombi (n = 16, 94%), and these thrombi were usually associated with an indwelling catheter (n = 11/16, 65%). The location of thrombi in the critical care cohort was evenly distributed: central venous n = 5, 42%; pulmonary artery n = 3, 25%; and cardiac/arterial n = 4, 33%.

Only 17 (37%) patients received antithrombotic therapy prior to tPA initiation, which included heparin, enoxaparin, or argatroban while 20 (43%) patients received concomitant heparin during tPA administration. There were 7 (15%) patients who received antiplatelet therapy (aspirin or clopidogrel) within 1 week prior to initiation of tPA.

There were 11 patients who received tPA within 30 days following a surgical procedure (mean 12.7 ± 7.8 days); 5 of these patients were started on tPA within 14 days of a preceding surgery. Ten of these 11 postsurgical patients (90%) were cardiac patients. The most common procedure was the bidirectional Glenn operation as part of single ventricle palliation (33%). Cardiac patients were more frequently intubated