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Thrombolysis in Pediatric Stroke (TIPS) study

Michael J Rivkin, MD[1], **Gabrielle deVeber, MD MHSc**[2], **Rebecca N Ichord, MD**[3], **Adam Kirton, MD MSc**[4], **Anthony Chan, MBBS**[5], **Collin A Hovinga, PharmD MS**[6], **Joan Cox Gill, MD**[7], **Aniko Szabo, PhD**[8], **Michael D Hill, MD**[9], **Kelley Scholz, MSW**[10], and **Catherine Amlie-Lefond, MD**[11]

[1]Departments of Neurology, Psychiatry and Radiology, Boston Children's Hospital

[2]Hospital for SickKids

[3]Children's Hospital of Philadelphia, Departments of Neurology and Pediatrics, Perelman School of Medicine of the University of Pennsylvania

[4]University of Calgary, Alberta Children's Hospital

[5]McMaster University

[6]Dell Children's Hospital

[7]Medical College of Wisconsin

[8]Division of Biostatistics, Medical College of Wisconsin

[9] Department of Clinical Neurosciences and Hotchkiss Brain Institute, University of Calgary

[10]Seattle Children's Research Institute

[11]Department of Neurology, University of Washington

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Introduction

Stroke is an important acute neurological condition in children with an annual incidence ranging from 2.3 to 13 per 100,000 children.[1-3] While most children who suffer stroke do not die of the acute disorder, the consequences of the brain injury are amortized over the lengthy lifespan that follows.[4-8] Potential for reduction in lifelong morbidity by timely and effective intervention with a thrombolytic agent such as tissue plasminogen activator (tPA) in children with acute arterial ischemic stroke (AIS) constituted the core rationale for study of tPA treatment of acute AIS in children. The perceived high potential for benefit following treatment justified assumption of risk for intracranial hemorrhage (ICH) following its use.[9] Since in adults, the risk of hemorrhage following tPA use was thought to be related to infarct volume, this principle was assumed for children. The known developmental trajectory of the

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fibrinolytic system includes lower levels of endogenous tPA and higher levels of plasminogen activator inhibitor 1 (PAI-1) in young children than are found in adults, and warranted a dose-finding study beginning at doses lower than that used in adults with incremental increase through the currently used adult dose of 0.9 mg/kg, and careful assessment of tPA pharmacokinetics.[10]

Currently, information regarding children treated with tPA consists of case reports, small case series, and hospital database documentation. Best practice for treatment of children with acute stroke has received little rigorous study. Clinical approach varies widely among centers, and reflects a dearth of research on which to base treatment protocols. Although tPA is not approved for use in childhood stroke, up to 2% of children with acute stroke are reported to have been treated with tPA in the United States despite lack of safety and efficacy data.[11-14]

In 2010 the NINDS funded the first prospective treatment trial in acute pediatric stroke, the Thrombolysis in Pediatric Stroke (TIPS) trial (NIH grant R01NS065848). TIPS reflected a multi-institutional, multidisciplinary design to determine safety, best dose and feasibility of treatment with intravenous (IV) tPA of children who present with AIS. Secondary aims comprised the determination of the pharmacokinetics of tPA in children and assessment of the 90 day clinical outcome among treated patients. TIPS was closed by the NIH in December, 2013 for lack of accrual. Herein, we summarize the lessons learned during the development and initial execution of the TIPS trial, the protocol synopsis, and the results of the challenges in implementation of the study.

The occurrence of symptomatic intracranial hemorrhage (SICH) following use of tPA in children with acute ischemic stroke constitutes a principal concern. When administered to adults according to NINDS guidelines, intravenous (IV) tPA therapy for AIS is associated with SICH in 6.4%.[15] This risk may be lower in younger patients as none of 48 young adults (16 to 49 years of age) treated with IV tPA for AIS developed SICH.[16] In adults with acute stroke, increasing hemorrhagic volume following IV tPA treatment correlated with increasingly poor neurologic outcome.[17]

During childhood, the fibrinolytic system is not yet mature.[10,18-20] Baseline free tPA concentration is decreased and PAI-1 concentration, an inhibitor of tPA, is increased, compared to adults.[20,21] In addition, children have an increased volume of distribution[22,23] and more rapid hepatic clearance suggesting they will clear tPA more quickly.[24] This raises the possibility that a higher dose of tPA than is used in adults may be needed to promote thrombolysis in children who present with acute AIS.

Most children with acute AIS present for care within 0-6 hours.[25,26] However, there can be significant in-hospital delay to diagnosis.[15,25-29] All TIPS sites were expected to establish and maintain acute stroke protocols for rapid diagnosis of acute stroke in children and ensure swift treatment with tPA in qualifying patients. Importantly, procedures for evaluation of children who present with symptoms of acute stroke were assessed at each site at the beginning of, during preparation for, and at site activation for TIPS.[30]

The challenges in protocol development for TIPS therefore encompassed: (1) the ethics of treatment children with potentially risky therapy for acute ischemic stroke; (2) the risk of SICH following treatment with tPA; (3) the effects of developmental hemostatic differences between children and adults that might affect the dosing, safety, and efficacy of tPA in acute pediatric arterial ischemic stroke; (4) tPA dose selection for children; (5) frequency and type of neuroimaging to be used in both initial assessment for tPA use and for follow-up after tPA administration; (6) inclusion and exclusion criteria; and (7) overcoming diagnostic delays to achieve eligibility for thrombolysis.

Methods

The TIPS study was an international multi-center, dose-adaptive, phase 1 cohort study. Study design spanned several years with input from members of the International Pediatric Stroke Study (IPSS), adult stroke specialists, and TIPS site investigators. Work in preparation for TIPS spanned 200 meetings over 3 years, including NINDS and FDA oversight in study design. As minimal safety and efficacy data on tPA use in childhood AIS exists, the most ethical way to proceed was through design of a consensus protocol for prospective enrollment and careful, complete follow-up, thereafter.

Children age 2 through 17 years of age who presented with acute AIS were eligible for enrollment to receive IV tPA if initiated within 4.5 hours of stroke onset (see Table 1 for inclusion and exclusion criteria). Importantly, at most centers, TIPS required confirmation of acute stroke by magnetic resonance imaging (MRI), using diffusion weighted imaging (DWI) to prove acute ischemic injury and magnetic resonance angiography (MRA) to identify some amount of arterial obstruction. In several centers, head computerized tomography (CT) showing a normal brain parenchyma or minimal early ischemic change and CT angiogram showing partial or complete arterial occlusion of the corresponding intracranial artery were used, consistent with pre-existing care pathways. Three dosing tiers were planned (0.75, 0.9, 1.0 mg/kg of IV tPA), with a maximum dose reached at 90 kg body weight. The IV tPA dose was to be given over one hour; ten percent of the total dose as a bolus over 5 minutes with the remaining 90% over the subsequent 55 minutes. The dosing tier for a given patient was determined using a Bayesian dose finding method, as below.[31] All patients underwent follow-up neuroimaging 24 hours after tPA infusion. Standard protocols were made available to all centers for the investigation and management of pediatric stroke. Guidelines for management of potential complications (ICH, systemic bleeding, angioedema, hypotension) of tPA treatment were provided to all centers. [Please see supplementary material on-line http://stroke.ahajournals.org]

Assays of free tPA activity, tPA antigen and plasminogen activator inhibitor-1 level were planned to determine tPA pharmacokinetics in children. Neuroimaging consisting of diagnostic and follow-up imaging obtained 24 hours following completion of the tPA dose was to be sent to the Imaging Core for review.

The clinical course following tPA treatment was to have been followed carefully. Patients were to be scored on the pediatric version of the NIH Stroke Scale (PedNIHSS)[32] at 2 hours, 12 hours, 24 hours, 36 hours, 48 hours, 7 days (or day of discharge if earlier) and at 3

months post-tPA administration. In addition, the Pediatric Stroke Outcome Measure (PSOM)[33,34] was to have been used at 7 days, and 3 months post-intervention. Finally, the King's Outcome Scale for Childhood Head Injury (KOSCHI)[35] and the Pediatric Evaluation of Disability Inventory (PEDI)[36] were planned at 3 months post-intervention.

Statistical methods

Dose limiting toxicity (DLT) was defined as presence within 36 hours of tPA administration of any of the following: (1) type 2 parenchymal hemorrhage (involving > 30% of the infarcted area; PH2)[37,38] or worse, regardless of whether or not it was associated with clinical deterioration; (2) any intracranial hemorrhage accompanied by neurological deterioration; or (3) any hemorrhage resulting in the need for transfusion, discontinuation of study drug, surgical evacuation of hemorrhage, or death. The target acceptable probability of dose-limiting toxicity was set at 10%. The maximal tolerated dose (MTD) was defined as the dose tier for which the estimated probability of dose-limiting toxicity is closest to 10% among the evaluated tiers for which the likelihood of having unacceptably high toxicity does not exceed 90%.

The study design was based on the Bayesian method of toxicity probability intervals[31] to guide the dose-modification process and the selection of the MTD among the three candidate dose tiers, with the entire process performed separately in two age group strata (2-10 years and 11-17 years). The final design is described below in short, with additional details of the parameter settings, dose-modification and final MTD estimation plans described in the on-line supplement. [Please see supplementary material on line http://stroke.ahajournals.org]

Up to 18 patients per stratum were expected to be recruited in cohorts of three starting at the lowest dose tier. The dose for each subsequent cohort chosen was based on the number of DLTs observed in all patients treated at the current dose using the cutoffs shown in Table 2 (Cutoffs for dose modification decisions). For example, if 6 patients (i.e. two cohorts) have already been treated at a given dose, then the next three patients would be enrolled at the next higher dose if no patients had a DLT, at the same dose if 1 patient had a DLT, and at the next lower dose if 2 or more patients had DLTs. In the latter case the dose will also be declared to have unacceptably high toxicity and the tier was to have been closed for any future enrollment. If the table called for escalation beyond the highest candidate tier or to a tier that had been previously closed due to excessive toxicity, then the dose would have been maintained at the current tier. If the lowest candidate tier was closed due to excessive toxicity, the study arm would have been stopped and no MTD selected. Otherwise, after 18 treated patients the MTD was to have been estimated. The design had a provision of enrolling up to 6 additional patients to ensure that the dose tier selected as the MTD had been evaluated in at least 6 patients.

Results

At the study's official start date, April 20, 2012, 22 primary sites were working towards study start-up. Of the 22 sites, 14 (63%) were activated at the time of study closure (12/21/2013). On average, these sites required 10 months to prepare for patient enrollment.

While several obstacles were encountered during the site start-up period, site preparation to diagnose and treat patients immediately constituted a formidable challenge the response to which has been reported previously.[30] Human subjects approval was often slow. The cost of study start-up at individual sites was an ongoing challenge, the most frequent of which was cost for tPA storage and immediately available preparation at study site pharmacies. At several institutions, the pK sample processing could only be done by a research support lab during weekdays, requiring study site teams to make provision to process samples outside of these times which included site-mandated training and certification to work in a study lab. Other challenges faced by sites included resolution of feasibility issues, dearth of dedicated research coordinator support, site requirements to establish data transfer agreements with Data Cores, and change in site principal investigator.

Of the twenty-two initially identified primary sites, 6 (27%) were unable to complete the start-up process for various reasons including feasibility, indemnity issues (international sites), or lack of dedicated coordinator time. In response to dropped sites, the TIPS Steering Committee instituted rolling site recruitment for participation in the TIPS study. Twelve additional sites were selected and at the time of study closure three had been activated, bringing the total number of activated sites to 17.

The 17 activated patient enrollment sites demonstrated the ability to triage and diagnose stroke promptly, obtain urgent diagnostic neuroimaging, and treat potential complications of stroke and thrombolysis, including coagulopathy, intensive care, neurosurgical emergencies. In addition, each had institutional-based guidelines for the evaluation and treatment of children who presented with acute AIS. Sites were active for a mean of 9 months (median 9.5 months, range 2-15 months). One child was enrolled but not treated due to a complication following extubation prior to tPA administration. Another 7 sites had completed preparation and were to be activated in January, 2014. The study was closed in December 2013 by the sponsor (NINDS) for lack of recruitment.

A total of 93 children aged 2-17 years were screened for TIPS, defined as a patient considered a possible candidate for the study based on the information provided to the study PI at initial contact (Figure 1). Almost half (43/93 or 46%) of children screened for possible acute stroke had a confirmed AIS. The remainder (50/93 or 44%) had a stroke mimic. Among children with confirmed stroke, 21 had a medical contraindication to receiving tPA including moyamoya arteriopathy (5 patients), anticoagulation treatment (5 patients), malignancy (3 patients), recent stroke (2 patients, one of whom was anticoagulated). Two patients had sickle cell disease, one of whom had a hemorrhagic infarct and one of whom had a PedNIHSS of 25. Two patients were excluded due to lack of occlusion on arterial imaging. Ten were outside the treatment window but presented within 12 hours, and at least 7 of these presented within approximately 5 hours. One arrived 3.5 hours after documented onset of AIS symptoms, but failed anesthesia, and one missed the window by 15 minutes due to a delay at the scanner. Six children were excluded based on pediatric NIHSS below the study cut-off of 6, ranging from 1-5, prior to revision downward of the PedsNIHSS to 4 or higher for patient inclusion in TIPS. Among children without confirmed stroke on MRI, three-quarters (31/41 or 76%) had a stroke mimic, defined as a child presenting with features compatible with ischemic stroke but subsequently proven by imaging to be caused by

something other than arterial ischemic stroke. Patients with moyamoya with presumed TIA but not stroke were included in this category. The remaining 10 had a non-benign mimic, defined as a patient not expected to return to baseline. (Table 3. Characteristics of 93 patients age 2 -17 years screened for TIPS)

Conclusion

The TIPS study arose from two major concerns in the pediatric stroke community. The first comprised safety of tPA administration to children. The second related to the absence of accurate outcome data for use of tPA in childhood stroke. These two key concerns persist. The TIPS study has begun to address the first issue by defining, through expert consensus and collective experience, safety criteria to guide the use of tPA in childhood. These criteria are available (refer to eSupplementary material) and could serve as a guideline for future studies in this area. These criteria still need to be tested, perhaps now in a funded international registry akin to the SITS-MOST[39] adult stroke registry in Europe. In the 10 months following study closure by the NINDS, former TIPS sites have continued to identify patients who would have been eligible for TIPS and have treated children with tPA using the TIPS protocol.

The TIPS study did not recruit pediatric ischemic stroke patients rapidly enough for continuation of funding by the NIH. Despite an enthusiastic and increasingly well established pediatric stroke community, the number of children with acute AIS who qualify for thrombolytic treatment within the therapeutic time window of 4.5 hours appears to be small. Even among the screened patients, nearly half had an alternate diagnosis and most of those with ischemic stroke presented a contraindication to treatment. Ultimately, only 1 of 93 screened children was enrolled into the study. It may be that pediatric regional centers for acute stroke evaluation and care would offer the best opportunity for efficient identification, transfer, and diagnosis leading to thrombolytic and other treatments for acute stroke in children. Such a regional center would work with other hospitals in the region to establish channels and protocols for rapid identification and transport of children believed to have acute arterial stroke to the regional primary pediatric stroke center. In such a plan some diagnostic evaluation may best be conducted at the referring hospital. Telemedicine methods may prove helpful. Thrombolytic treatment could in some cases begin during transport to the pediatric primary stroke center.

The difficulties of enrollment in TIPS suggest that establishing an acute stroke program must precede a prospective acute interventional clinical trial in acute childhood stroke. Routine stroke recognition, rapid diagnosis and management are not widespread in the community at large. The insitution of TIPS led to the development and refinement of Primary Pediatric Stroke centers able to provide acute care to children with acute stroke and it is hoped that these guidelines will allow children to be represented in future trials of acute stroke intervention.[30] The pediatric stroke community must now continue to work together to ensure that if tPA is given in childhood ischemic stroke, that standard safety protocols are not only established but followed and outcomes are collected and used to guide further recommendations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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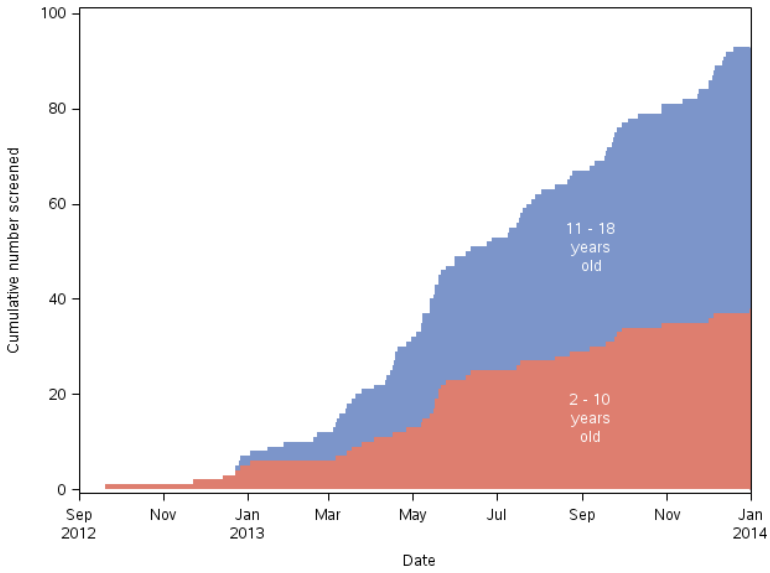

Figure 1.
Children screened for TIPS

Table 1

TIPS Inclusion and Exclusion Criteria

Inclusion Criteria
Age 2 to 17 years
Acute ischemic stroke defined as acute onset neurological deficit with a pattern consistent with arterial ischemia
PedNIHSS ≥ 4 and ≤ 24
Treatment can be adminsitered within 4.5 of stroke onset
Radiological confirmation of an acute ischemic stroke by:
(a) MR showing acute stroke on diffusion imaging plus MRA showing arterial partial or complete arterial occlusion of the corresponding intracranial artery
(b) CT and CT angiogram confirmation showing a normal brain parenchyma or minimal early ischemic change plus partial or complete arterial occlusion of the corresponding intracranial artery
No evidence of any intracranial hemorrhage.
Children with seizure at onset may be included as long as they fulfill the criteria above
Exclusion Criteria
Unknown time of symptoms onset
Pregnancy
Clinical presentation suggestive of SAH even if brain imaging is negative for blood.
Patient who would decline blood transfusion if indicated
History of prior intracranial hemorrhage
Known cerebral arterial venous malformation, aneurysm, or neoplasm
Persistent Systolic Blood Pressure > 15% above the 95th percentile for age while sitting or supine
Glucose <50 mg/dl (2.78 mmol/l) or > 400 mg/dl (22.22 mmol/l)
Bleeding diathesis including platelets < 100,000, PT > 15 sec (INR > 1.4) or elevated PTT > upper limits of the normal range.
Clinical presentation consistent with acute myocardial infarction (MI) or post-MI pericarditis that requires evaluation by cardiology prior to treatment
Prior stroke, major head trauma, or intracranial surgery within the past 3 months
Major surgery or parenchymal biopsy within 10 days (relative contraindication)
Gastrointestinal or urinary bleeding within 21 days (relative contraindication)
Arterial puncture at noncompressible site or lumbar puncture within 7 days (relative contraindication). Patients who have had a cardiac catheterization via a compressible artery are not excluded.
Patient with malignancy or within 1 month of completion of treatment for cancer
Patients with an underlying significant bleeding disorder. Patients with a mild platelet dysfunction, mild von Willebrand Disease or other mild bleeding disorders are not excluded.
Stroke related exclusion criteria
Mild deficit (PedNIHSS < 4) at start of tPA infusion or at time of sedation for neuroimaging, if applicable.
Severe deficit suggesting very large territory stroke, with pre-tPA PedNIHSS > 24, regardless of the infarct volume seen on neuroimaging.
Stroke suspected to be due to subacute bacterial endocarditis, moyamoya, sickle cell disease, meningitis, bone marrow, air or fat embolism.
Previously diagnosed primary angiitis of the central nervous system (PACNS) or secondary CNS vasculitis. Focal cerebral arteriopathy (FCA) of childhood is not a contraindication.
Neuro-imaging related exclusions:
Intracranial hemorrhage (HI-1, HI-2, PH-1 or PH-2) on pretreatment head MRI or head CT

Intracranial dissection (defined as at or distal to the opthalmic artery)
Large infarct volume, defined by the finding of acute infarct on MRI involving 1/3 or or more of the complete MCA territory involvement
Drug Related exclusions:
Known allergy to recombinant tissue plasminogen activator
Patient on anticoagulation therapy must have INR ≤ 1.4
Patient who received heparin within 4 hours must have aPTT in normal range
LMWH within past 24 hours (aPTT and INR will not reflect LMWH effect)

Table 2

Cutoffs for dose modification decisions

Cumulative number of patients at the dose	Cumulative number of DLTs for each decision		
	Escalate to next tier	Stay at current tier	De-escalate and close tier
3	0	1	2+
6	0	1	2+
9	0	1-2	3+
12	0-1	2	3+
15	0-1	2-3	4+
18	n/a	n/a	4+

Table 3

Characteristics of 93 patients age 2 -17 years screened for TIPS

Screens	No (%)	Reason patient not enrolled	
43 (46%) confirmed stroke	21(22%)	Medical contraindications ± time to presentation > 12 hours	
	5(5%)	PedNIHSS < 6 (2,2,3,4, < 6)	
	10(11%)	Diagnosed at 4.5 to 12 hours	
	4(5%)	PedNHSS < 6 and outside time window	
	2(2%)	Without clot visualized	
	1(1%)	Not applicable, child was enrolled	
50 (54%) stroke mimics	38(41%)	Benign mimic	
	12(13%)	Non-benign mimic	2-hemorrhagic stroke
			3-mass lesion
			2-infection
			2-methotrexate toxicity
			2-posterior reversible encephalopathy syndrome