Endovascular therapy in children with acute ischemic stroke

Review and recommendations

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ABSTRACT

This review provides a summary of the currently available data pertaining to the interventional management of acute ischemic stroke in children. The literature is scarce and is lacking much-needed prospective trials. No study in the literature on the well-established systemic or local thrombolysis trials has included children. Mechanical thrombectomy trials using clot retriever devices have also excluded patients younger than 18 years. The current review is limited to case series of interventional acute ischemic stroke therapy in children and the potential future of endovascular ischemic stroke therapy in this patient population. Recommendations in this review represent the opinion of the authors, based on review of the limited literature covering endovascular acute ischemic stroke therapy in children. **Neurology® 2012;79 (Suppl 1):S158-S164**

GLOSSARY

AIS = acute ischemic stroke; **IA** = intra-arterial; **ICA** = internal carotid artery; **MCA** = middle cerebral artery; **TIPS** = Thrombolysis in Pediatric Stroke; **tPA** = tissue plasminogen activator.

The principal goal of acute endovascular therapy for arterial ischemic stroke (AIS) is prompt recanalization of the occluded vessel and restoration of blood flow to the ischemic brain. In adults with AIS, IV administration of tissue plasminogen activator (tPA) within 3 hours of symptom onset is associated with improved 3-month¹ and 1-year clinical outcomes² and is the only approved medical treatment for this condition.³ More recent studies demonstrate safety and suggest benefit from IV tPA up to 4.5 hours after symptom onset.⁴ Patients presenting outside this therapeutic window or those with contraindications to IV tPA may benefit from intra-arterial (IA) pharmacological thrombolysis^{5,6} or mechanical thrombolysis/thrombectomy with a variety of approved or investigational endovascular devices.⁷⁻⁹

Following AIS, 3% to 6% of children will die, 25% will have recurrent stroke, and 70% will survive with life-long disability,¹⁰⁻¹² resulting in decades of enormous personal and societal burden. There are no published clinical trials examining IV, IA, or endovascular mechanical thrombolytic strategies in children with AIS. However, despite age-related differences in cerebrovascular, coagulation, and fibrinolytic systems in children¹³ and lack of established guidelines for thrombolytics in childhood AIS,¹⁴ numerous cases have been reported in the literature.¹³ The Thrombolysis in Pediatric Stroke (TIPS) trial will establish the safety and feasibility of IV tPA in children with AIS,¹⁵ but there have been no such studies addressing the safety or efficacy of IA thrombolysis or endovascular therapies in the management of pediatric AIS, and no formal guidelines exist.

The objectives of this report are to summarize the reported literature on the use of endovascular thrombolytic therapies in children with AIS and to address the potential role of endovascular techniques in the management of AIS in children.

METHODS All reported cases of pediatric AIS in the English-language literature that were treated with endovascular thrombolytic strategies were reviewed. Cases were identified by a PubMed search from 1965 to 2011 using these key words: child, pediatric, stroke,

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thrombolysis, tissue plasminogen activator, and endovascular. Case reports of IA pharmacologic thrombolytics (tPA, urokinase, streptokinase) and mechanical thrombolytic approaches (such as guidewire maneuvers, clot retrieval/aspiration devices, and balloon angioplasty) were included. Reports describing the use of endovascular stents or other devices were included only if these procedures were performed in the setting of planned thrombolytic therapy for pediatric AIS. Studies were analyzed for variables including demographic data, stroke risk factors, vessels occluded, time to initiation of endovascular treatment, use of IV thrombolysis in addition to IA treatment, endovascular therapies used, procedural complications, and postprocedural hemorrhage. Recanalization was classified as complete (no residual filling defect in any vessels), incomplete (residual filling defect seen, but with improvement as compared with presentation), and none (no change in vessel occlusion). Hemorrhage was classified as symptomatic if it was associated with deterioration in the patient's clinical examination. Studies were excluded from analysis if they did not report on 4 of the following 5 variables: time to initiation of endovascular treatment, use of IV thrombolysis in addition to IA treatment, endovascular therapies used, procedural complications, and postprocedural hemorrhage.

RESULTS A total of 34 cases of pediatric AIS treated with endovascular thrombolytic therapies were identified in the literature (details summarized in the table). This cohort included 18 males and 16 females, with a mean age at the time of treatment of 10.9 years (range, 2–18). Systemic risk factors for AIS were identified in 23 of 34 patients (67.6%). Cerebrovascular risk factors were identified in 12 of 34 patients (35.3%). The mean time from the onset of symptoms to endovascular therapy was 14.0 hours (range, 2–72). Only 1 patient underwent treatment with IV tPA prior to endovascular therapy. Endovascular therapies included IA thrombolysis alone ($n = 23$), IA thrombolysis + mechanical thrombolysis ($n = 9$), and mechanical thrombolysis alone ($n = 2$). One patient underwent definitive treatment of primary vessel pathology using endovascular stent placement.

Recanalization was complete in 12/34 cases (35.2%), incomplete in 13/34 cases (38.2%), and absent in 3/34 cases (8.8%); recanalization status was not reported in 6/34 cases (17.6%). Complications (including periprocedural complications and postprocedural hemorrhage) occurred in a total of 10/34 cases (29.4%). Postprocedural intracranial hemorrhage occurred in 8/34 patients (23.5%), although only 1 of these hemorrhages was symptomatic (2.9% of all cases).

DISCUSSION As demonstrated in the table, the results of our literature search highlight the marked variability in the use of endovascular thrombolytic therapies in pediatric AIS and underscore the critical need for controlled clinical trials and formal guidelines in this population. Across the 35 reported cases

we calculated a partial or complete recanalization rate of 74% and a complication rate of 29%. However, because clinical outcomes could not be assessed, the clinical relevance of these findings is unknown. Moreover, there is undoubtedly publication bias, with underreporting of cases with fatal or severe complications vs relatively successfully treated cases. This trend has been observed in the use of IV tPA in childhood stroke, when data from published cases were compared to “real-world” registry.¹³

Future studies in the endovascular management of pediatric AIS must take into consideration the important factors that differentiate pediatric AIS from its adult counterpart in terms of etiology, physiology, and natural history (figure). Moreover, pediatric AIS occurs in the context of underlying age-related differences in cerebrovascular anatomy and physiology^{13,15} and in developmental maturation of the hematologic, hemostatic, and fibrinolytic^{16,17} systems throughout infancy and childhood. For these and other reasons, tPA dosing has not been rigorously determined in children, and no endovascular mechanical thrombolytic device has been tested or approved for use in children. Moreover, when stent placement accompanies other endovascular treatments in cerebral arteries in children, the durability over the remaining decades of life is unknown and presents an additional concern.

The newly launched TIPS trial is an NIH-funded 5-year, prospective, open-label trial that will examine the safety and feasibility of IV tPA in children (aged 2–17 years) with AIS.¹⁵ An adaptive dose-finding method will be applied to escalate across 3 dose levels of 0.75 mg/kg, 0.9 mg/kg, and 1.0 mg/kg, within 2 age groups: 2–10 years and 11–17 years. Although the TIPS trial represents an important step toward establishing evidence-based standards in pediatric AIS management, there are presently no formal guidelines addressing the role of endovascular therapies in this population. Given the lack of safety and efficacy data for tPA, the use of tPA outside of a clinical trial is discouraged.^{14,18}

Until Class I data are available to support the use of endovascular thrombolytic therapies in children with AIS, the management of these challenging cases must be individualized, weighing the natural history of the disease not only against the inherent risk of the procedure but also taking into consideration the experience of the neurointerventional team in treating children. This latter point is critical: several recent studies have demonstrated a remarkable level of safety of cerebral angiography in the hands of experienced practitioners.^{19,20} But conversely, cases where mismanagement resulted from a neurointerventionalist approaching the pediatric patient as a small

Table Summary of the clinical characteristics, treatment details, and outcomes for children with AIS managed with endovascular thrombolytic therapy, as reported in the literature

Reference	Age, y	Sex	Systemic risk factors	Cerebrovascular risk factors	Vessels occluded	Time to treatment, h	Endovascular treatment (dosing)	Recanalization	Postprocedural hemorrhage or complication
Barnwell et al. (1994) ²¹	16	F	NA	None	BA	48	IA UK	Complete	None
Barnwell et al. (1994) ²¹	12	F	Atrial myxoma	None	L MCA	7	IA UK	None	None
Larner et al. (1998) ²²	18	F	Migraine, smoking, oral contraceptives	None	BA	12	IA streptokinase	None	Symptomatic hemorrhage
Hoffman et al. (1999) ²³	9	M	Trauma	R VA dissection	BA, R VA	5	IA UK	Incomplete	None
Kitzmuller et al. (1999) ²⁴	2.75	M	Cardiac	None	L ICA, MCA	2.5	IA tPA	Complete	Asymptomatic hemorrhage
Gruber et al. (2000) ²⁵	6.6	M	Cardiac	None	R MCA	2	IA tPA, mechanical (guidewire)	Complete	None
Cognard et al. (2000) ²⁶	8	M	None	L VA dissection	BA, L PCA	36	Mechanical (balloon angioplasty), IA UK	Incomplete	None
Sungarian & Duncan (2003) ²⁷	9	M	Trauma	R VA dissection	BA	6	IA UK	Complete	None
Sungarian & Duncan (2003) ²⁷	10	F	None	Bilateral VA pseudoaneurysms	BA	4.8	IA UK	Complete	Asymptomatic hemorrhage/contrast extravasation
Golomb et al. (2003) ²⁸	17	F	Substance abuse, deep venous thrombosis	Diagnostic angiogram	L MCA	2.2	IA tPA	Complete	Limb ischemia requiring amputation
Kirton et al. (2003) ²⁹	15	M	None	None	BA	20	IA tPA, mechanical (guidewire, Attractor-18 clot retriever, Retriever-18 endovascular snare), balloon angioplasty	Incomplete	None
Rosman et al. (2003) ³⁰	18	F	Migraine, oral contraceptives	None	BA	72	IA tPA	Complete	Asymptomatic hemorrhage
Zaidat et al. (2005) ³¹	16	M	Cardiac	None	BA	20	Mechanical (IN-TIME Retrieval System), balloon angioplasty	Incomplete	None
Bourekas et al. (2005) ³²	15	M	None	None	L supraclinoid ICA	5.75	IA UK	Complete	Asymptomatic hemorrhage
Benedict et al. (2007) ³³	2	F	Cardiac	None	R MCA/ACA	4.3	IA tPA	Incomplete	Increased pleural effusion
Grigoriadis et al. (2007) ³⁴	6	M	Trauma	L VA dissection	BA	44	IA UK, mechanical (crossing thrombus with microsystem), balloon angioplasty	Incomplete	None
Bhatt et al. (2008) ³⁵	3	F	Cardiac	None	BA	18	IA tPA	Incomplete	None
Tsivgoulis et al. (2008) ³⁶	6	M	Cardiac	None	R ICA	3.42	IA Reteplase, mechanical (Merci Retriever, balloon migration advancement of clot into R ACA A1) ^a	Incomplete	None
Amlie-Lefond et al. (2009) ¹³	5	M	Cardiac	None	L ICA	4	IA tPA	NA	NA
Amlie-Lefond et al. (2009) ¹³	7	F	None	None	BA	24	IA tPA	NA	NA
Amlie-Lefond et al. (2009) ¹³	8	F	Cardiac	L MCA stenosis	L ACA	3.8	IA tPA	NA	NA
Amlie-Lefond et al. (2009) ¹³	15	F	None	Arteriopathy (dissection)	R ICA	4	IA tPA	NA	Asymptomatic hemorrhage
Amlie-Lefond et al. (2009) ¹³	15	M	Arteriopathy (vasculitis)	Vasculitis	L MCA	7.5	IA tPA	NA	NA

—Continued

Table Continued

Reference	Age, y	Sex	Systemic risk factors	Cerebrovascular risk factors	Vessels occluded	Time to treatment, h	Endovascular treatment (dosing)	Recanalization	Postprocedural hemorrhage or complication
Amlie-Lefond et al. (2009) ¹³	15	F	None	Arteriopathy (dissection)	R MCA	5	IA tPA	NA	Asymptomatic hemorrhage
Janmaat et al. (2009) ³⁷	4	M	Arteriopathy (vasculitis), infection	Vasculitis	BA	60	IA UK	Incomplete	None
Arnold et al. (2009) ³⁸	12	M	Infection	None	L ICA, MCA M1, ACA A1	5	IA UK	Incomplete	None
Arnold et al. (2009) ³⁸	9	M	Infection	None	BA, PCA	12	IA UK	Incomplete	None
Tan et al. (2009) ³⁹	12	F	Infective endocarditis	None	L ICA, MCA	6	IA tPA	Incomplete	None
Felker et al. (2010) ⁴⁰	14	M	None	None	L MCA	9	IA tPA, mechanical (MERCIA retriever device)	None	Coil dislodged from device with 100% M1 occlusion, asymptomatic hemorrhage day 11
Grunwald et al. (2010) ⁴¹	16	F	None	None	BA	8	IA tPA, mechanical (Penumbra System)	Complete	None
Grunwald et al. (2010) ⁴¹	7	M	Cardiac	None	L ICA, MCA	3	Mechanical (Penumbra System)	Complete	None
Grunwald et al. (2010) ³⁹	16	F	Oral contraceptives	None	L MCA M1	3.5	IA tPA, mechanical (Phenox device)	Complete	None
Lai et al. (2010) ⁴²	12	F	None	L paraclinoid ICA dissection	L ICA, MCA	4	IA UK, mechanical (balloon angioplasty of dissection, deployment of 3 × 12-mm balloon-expandable stent)	Complete	None
Chen et al. (2010) ⁴³	15	M	Infection, smoker	None	BA	5.3	IA UK	Incomplete	None

Abbreviations: ACA = anterior cerebral artery; BA = basilar artery; IA = intra-arterial; ICA = internal carotid artery; MCA = middle cerebral artery; NA = not available; PCA = posterior cerebral artery; SK = streptokinase; tPA = tissue plasminogen activator; UK = urokinase; VA = vertebral artery.

^a Patient was treated with IV tPA prior to endovascular thrombolysis.

adult are unfortunately not rare, with potentially devastating consequences. Our presumption here is referral of pediatric AIS cases, with their inherent treatment urgency, to centers with significant neuro-interventional experience in children.

Although promising results of endovascular thrombolytic therapies in adults cannot be casually generalized to children, they can be used to cautiously generate guidelines for the management of pediatric cases. On the basis of this experience, we consider only endovascular thrombolytic therapies in children with AIS, as described next. We stress that what follows are recommendations based on the opinions of the authors, resulting from cautious extrapolation of adult data and from interpretation of the pediatric literature reviewed here. By the American Heart Association Stroke Council's Level of Evidence grading algorithm, what follows is Class IIb.

Patient eligibility. Although the decision to treat and the lower age cutoff for eligibility ultimately fall on the multidisciplinary stroke team at the treating institution, we recommend that only children with significant and potentially disabling neurologic deficits

(pediatric NIH Stroke Scale scores ≥ 10 and ≤ 30) and radiologically confirmed occlusion of a dominant cerebral artery should be considered for endovascular thrombolytic therapy. The table attests to the well-known diagnostic difficulty in differentiating AIS from other causes of acute neurologic change in children, such as seizure, postictal sequelae, and complex migraine, leading to delayed diagnosis of AIS; the mean time from symptom onset to treatment in the published pediatric cases was 14 hours, and only a single case out of 34 was a candidate for IV tPA. We thus consider it vital that every case be assessed by a pediatric stroke neurology team. If possible, demonstration of absence of a large region of MRI diffusion restriction would be helpful, though we do not recommend abstaining from endovascular treatment if an MRI is not obtainable, because in many cases the insistence on MRI would add unacceptable delay. Moreover, in the presence of both persisting focal neurologic deficit and occlusion of a corresponding cerebral artery (which can be clearly defined on initial angiography), the risk of treating non-AIS is minimal.

Frontal angiographic views of a right common carotid (A and B, pretreatment) and a right ICA injection (C and D, intra- and post-treatment, respectively) in a 14-year-old boy with a history of cardiomyopathy and arrhythmia who presented with acute left hemiparesis. He was not a candidate for treatment with tPA. Early (A) and late (B) arterial phases pretreatment demonstrate no flow above the ophthalmic artery. Threatened large-territory hemispheric ischemia in a young patient such as this poses a risk of massive edema and herniation. Arterial phase image after use of the 0.041 Penumbra suction microcatheter and separator at the ICA terminus (C) demonstrates opacification of the ICA terminus, the posterior communicating artery, the posterior cerebral candelabra, and the proximal anterior cerebral artery. Arterial phase image after use of the 0.032 Penumbra system in the M1 middle cerebral segment demonstrates opacification of the ICA terminus, the anterior cerebral candelabra, the M1 segment, and the superior division of the MCA.

Periprocedural heparin. All patients should have a baseline activated clotting time determined prior to heparin administration. After placement of the femoral sheath, our patients receive a bolus of IV heparin (50 U/kg) prior to diagnostic cerebral angiography. We titrate heparin infusion during the case to sustain the activated clotting time at 200 to 350 throughout, rechecking every 45 minutes, and supplementing as needed.

Diagnostic cerebral angiography. We use a micropuncture set for vascular access in all cases. For all patients under 15 kg and for larger patients in whom a mechanical thrombectomy is not planned, we use a 5F sheath with a 5-Fr Envoy catheter. The sheath, guiding catheter, and microcatheters are continuously flushed via a pressurized bag of heparinized saline (1,000–4,000 U heparin/L, depending on the age and weight of the patient). We obtain a baseline diagnostic angiogram demonstrating the entire circle of Willis prior to any intervention, in order to fully visualize the occlusion and assess all avenues of collateral flow.

IA thrombolysis vs endovascular mechanical thrombolysis/thrombectomy. Review of the table reveals that in nearly a third of all reported pediatric AIS cases treated via endovascular means, mechanical thrombectomy was used (11/34 cases), whereas in 23/34, IA thrombolytic alone (tPA or urokinase) was administered. Eight of the 34 total cases were complicated by intracranial hemorrhage (albeit asymptomatic in 7/8). Strikingly, mechanical thrombectomy was asso-

ciated with only a single case of these 8 incidents of hemorrhage, yielding a hemorrhage rate of 1/11 or 9.1%, for cases treated mechanically; moreover, in that single case, IA tPA was administered as well. Conversely, IA thrombolytic alone was administered in 7/8 of the reported cases of hemorrhage, yielding a hemorrhage rate of 7/23 or 30.4%, for cases treated with IA thrombolytic. As such, we approach the use of IA tPA with caution and try whenever possible to use mechanical approaches alone or else to mechanically augment the use of IA tPA by such means as carefully passing the microwire and microcatheter through the thrombus several times in succession while injecting intrathrombus tPA. In the setting of familiarity with the gentleness of traction and great care needed in pediatric cases to avoid vessel injury, such mechanical means may be safer than simple IA injection of tPA alone. Furthermore, we conservatively limit the IA tPA dose to 0.2 mg/kg, with a maximum dose of 12 mg. An example of the use of the Penumbra device for safe mechanical thrombectomy in a 14-year-old boy is shown in the figure.

Post-treatment management. Following thrombolytic therapy or thrombectomy, we undertake control angiography via the guide catheter in the occluded vessel to assess vessel recanalization, potential vasospasm, dissection, or contrast extravasation, as well as to ascertain whether thrombus fragmentation and distal embolization have occurred. Once the heparin infusion is discontinued and an activated clotting time of ≤ 200 is achieved, the femoral sheath is re-

moved. The patient is transferred intubated to the intensive care unit, with detailed neurologic assessment and attempted extubation typically deferred until the next day. If possible, MRI, with fluid attenuation inversion recovery, diffusion, and MR angiography sequences, are obtained in the interim. Meticulous treatment in the intensive care unit, with particular attention to euglycemia and euthermia, is initiated. Assuming that flow was reestablished in the occluded vessel, we target mean and systolic blood pressures at 70% to 100% of the expected mean values for age.

CONCLUSION Although IV and endovascular thrombolytic therapies have revolutionized the management of AIS in adults, there are no published clinical trials or prospective studies examining IV, IA, or endovascular mechanical thrombolytic strategies in children with AIS. Until further data are available, the use of thrombolytic therapies in children with AIS must be considered experimental, especially in young, preschool children, recognizing that safety and efficacy are currently unknown. Optimal care of these children requires a considered and cautious approach by a neurointerventional team in close collaboration with pediatric stroke neurologists or, when not available, with a team including a pediatric neurologist and adult stroke neurologist, where at least 1 member of the team has extensive pediatric stroke experience, in order to minimize adverse outcomes. The recommendations in this review represent the opinions of the authors based on review of the limited literature covering endovascular therapy for acute ischemic stroke in children.

NOTE ADDED IN PROOF

As we attempted here a definitive review of all published reports of intra-arterial intervention for acute ischemic stroke in children, we note that 2 references were published during the time between acceptance of the final version of this manuscript and publication, and are thus not included in the body of the paper.^{44,45} Both reports describe successful recanalization of basilar artery occlusions, the first by purely mechanical means and the second by combined intra-arterial thrombolysis and mechanical thrombus disruption. In neither case were there procedure-related adverse events.

AUTHOR CONTRIBUTIONS

Dr. Ellis: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, and statistical analysis. Dr. Amlie-Lefond: drafting/revising the manuscript, analysis or interpretation of data. Dr. Orbach: drafting/revising the manuscript, analysis or interpretation of data, study supervision.

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DISCLOSURE

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performs neurointerventional radiology 60% of the time at Children's Hospital Boston; receives research support from Children's Hospital Radiology Foundation for fMRI-EEG research on epilepsy patients; and receives research support from ASNR/ISMRM for fMRI-EEG research on epilepsy patients. **Go to Neurology.org for full disclosures.**

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