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Thrombolysis in Childhood Stroke

Report of 2 Cases and Review of the Literature

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Background and Purpose—No controlled, randomized trial has investigated whether intravenous, intra-arterial (IAT), or mechanical thrombolysis is beneficial in children with ischemic stroke. We report 2 children who underwent IAT for acute ischemic stroke and include them in a review about intravenous thrombolysis, IAT, and mechanical thrombolysis for childhood stroke.

Methods—We searched in MEDLINE and EMBASE for studies that reported on treatment of childhood stroke with intravenous thrombolysis, IAT, or mechanical thrombolysis in the presence of occlusion of the basilar artery, sphenoidal, or insular middle cerebral artery. To be included in this review, the following findings had to be reported: (1) stroke severity at presentation; (2) cerebral imaging findings before thrombolysis; (3) time to treatment; (4) dose of the thrombolytic agent; (5) pre- and postinterventional angiographic findings in IAT; and (6) outcome assessed at hospital discharge or within 12 months after thrombolysis.

Results—Adequate data were available in 17 children (including our 2 own cases) who underwent intravenous thrombolysis (n=6), IAT (n=10), or mechanical thrombolysis (n=1). No symptomatic intracranial hemorrhage occurred, but 2 asymptomatic intracranial hemorrhages were present. Sixteen children (94%) survived, and 12 (71%) had a good outcome (modified Rankin Scale score 0 or 1).

Conclusions—The available data about thrombolysis in pediatric stroke are limited. They suggest that this treatment may be beneficial in children with ischemic stroke. Controlled, randomized trials are needed to determine whether thrombolysis is useful in childhood stroke. (*Stroke*. 2009;40:801-807.)

Key Words: acute stroke ■ stroke in children ■ thrombolysis

Pediatric stroke is defined as a stroke occurring in patients who are between 1 month and 18 years of age.¹ It has an incidence of 2.5 to 13 per 100 000 children per year and is more common in males and blacks.¹⁻⁴ Although this rate is much lower compared with adults, pediatric stroke has an important morbidity, because at least 50% of children are left with significant neurological deficits or epilepsy.⁵⁻⁷ The resulting socioeconomic burden is substantial due to the loss of decades of productive years of life and the need for long-term care and therapies.⁸ Furthermore, mortality in childhood stroke ranges from 7% to 28%.^{9,10} Controlled, randomized trials (CRT) and meta-analyses have proven the efficacy of intravenous thrombolysis (IVT)^{11,12} and intra-arterial thrombolysis (IAT)^{13,14} in adult patients with acute ischemic stroke. In contrast, no CRT looking at thrombolysis of childhood stroke has yet been conducted.

We report 2 children who underwent IAT for acute ischemic stroke and a review of thrombolytic treatment for childhood stroke.

Methods

Patients

Two children who underwent IAT in the University Hospital of Bern, Switzerland, in 1997 and 2007 are reported.

Search Strategy and Selection Criteria for the Literature Review

We searched in MEDLINE (January 1966 to September 2007) and EMBASE (January 1980 to September 2007) and checked all relevant papers for additional eligible studies. The following key words were used: stroke, childhood, child, pediatric, thrombolysis, thrombolytic therapy, plasminogen activator, urokinase, angioplasty, emergency treatment, cerebral revascularization, brain revascularization, basilar artery, and middle cerebral artery. We analyzed case reports, case series, observational and case-control studies, and CRTs that reported on treatment of ischemic childhood stroke with IVT or IAT in the presence of occlusion of the basilar artery (BA), sphenoidal, or insular middle cerebral artery (MCA). To be included in this review, the following findings had to be reported: (1) stroke severity at presentation; (2) cerebral imaging findings prior to

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thrombolysis; (3) time from stroke to treatment onset; (4) dose of the thrombolytic agent; (5) pre- and postinterventional angiographic findings in children treated with IAT; and (6) outcome assessed at hospital discharge or within 12 months after thrombolysis. Baseline National Institute of Health Stroke Scale (NIHSS) score and modified Rankin scale score at follow-up were estimated from the available data.

Results

Patient 1

A 12-year-old boy with an uneventful familial and medical history presented with global aphasia and right hemiplegia 14 days after a streptococcal pharyngeal infection. Neurological examination performed 3 hours after symptom onset revealed a conjugate gaze deviation to the left, right hemiplegia, hemihypesthesia, and extensor plantar sign. The NIHSS score was 22. Laboratory examinations were normal. Cerebral CT showed a hyperdense left MCA and early signs of infarction in its territory. Digital subtraction angiography (DSA) showed occlusions of the left terminal (C1) internal carotid artery (ICA), sphenoidal MCA, and the precommunicating anterior cerebral artery. Leptomeningeal collateral circulation was poor, and no lenticulostriate arteries were visualized on the left side. Five hours after symptom onset, the patient was treated under general anesthesia with IAT using a Fast Tracker (Target Therapeutics) microcatheter, which was navigated into the occluded vessel and urokinase 750 000 IU (UK; UK HS Medacc) was infused into the proximal end of the thrombus over 60 minutes. After IAT, 250 mg intravenous aspirin was given. Repeat DSA showed partial recanalization (thrombolysis in myocardial infarction Grade 2) of C1 ICA and precommunicating anterior cerebral artery, but the MCA remained occluded. Ten hours after thrombolysis, the patient sustained a generalized seizure and was treated with intravenous phenytoin. The next day, neurological examination showed an impaired consciousness, persisting gaze deviation to the left, global aphasia, and right hemiplegia. An electroencephalogram showed focal slowing in the left hemisphere without epileptic activity. Cerebral CT demonstrated a complete MCA infarction with midline shift and a persisting hyperdense MCA but no intracranial hemorrhage (ICH). A craniectomy was not performed, and the boy died the next day. Etiology of stroke remained undetermined.

Patient 2

One week after a viral pharyngeal infection, a 9-year-old, previously healthy boy with an uneventful familial history suddenly experienced gait ataxia and became somnolent. Two hours later, he had a generalized seizure and was admitted to the emergency department of another hospital. Laboratory examinations, including a search for vasculitis and metabolic disorders, were normal. Cerebral CT showed a hypodensity in the territory of the right posterior cerebral artery. After clinical deterioration with more severe impairment of consciousness, the boy was transferred to our hospital. On admission, clinical neurological examination revealed impaired consciousness, severe spastic tetraparesis, and intermittent decerebrate posturing. The NIHSS score on admission

was 22. Brain MRI, including diffusion-weighted and apparent diffusion coefficient maps, revealed multiple acute infarcts in the left cerebellum, right posterolateral pons, left paramedian anterior pons, and bilateral deep and superficial posterior cerebral artery territories. Three-dimensional time-of-flight MR angiography and DSA showed occlusions of the middle and distal segments of the BA and the left posterior cerebral artery. DSA revealed moderate collateral flow with reversed filling of the left superior cerebellar artery but depicted no brain stem perforator. Twelve hours after symptom onset, the patient was treated under general anesthesia with IAT using a Renegade microcatheter. Urokinase at a dose of 750 000 IU was infused directly into the proximal end of the thrombus over 60 minutes. After IAT, intravenous aspirin (250 mg) was given followed by 100 mg oral aspirin per day. Repeat DSA showed partial recanalization (thrombolysis in myocardial infarction Grade 2) of the BA, and brainstem perforators reappeared. The next day, neurological examination revealed normal consciousness, limb ataxia, and a right extensor plantar sign. Transesophageal echocardiography and 24-hour electrocardiogram were normal. Stroke etiology remained undetermined. Follow-up MRI on Day 19 showed multiple small T2-hyperintense infarcts in the left cerebellum, the left paramedian pons, and thalamus and both medial occipital lobes. Consciousness and tetraparesis improved rapidly, and the child was able to walk without assistance after 10 days. Neurological and neuropsychological follow-up examination after 3 months showed marked fatigue, mild dysphasia, right hemiparesis, and left hemiataxia. Neuropsychological evaluation showed moderate deficits of attention and executive functions. The modified Rankin Scale (mRS) score was 2. The child was able to attend his former school class.

Literature Review

No CRT and no case-control study were identified.

Excluded Studies

The largest series reported 46 children who were entered in the US Nationwide Inpatient Sample between 2000 and 2003 with International Classification of Diseases codes for ischemic stroke and underwent thrombolysis (IVT, n=24 [52%]; IAT, n=19 [41%]; unknown, n=3 [7%]).⁸ The authors were not able to assess stroke severity at presentation, cerebral imaging findings, time to treatment, dose of the thrombolytic agent, pre- and postinterventional angiographic findings in children who underwent IAT, and clinical outcome.⁸ Furthermore, risk factors and potential stroke etiologies were not reported for most of the 46 children.⁸ Due to these limitations, this study was not included. However, it is important to mention that no symptomatic ICH was reported in children who underwent thrombolysis compared with 0.8% of symptomatic ICH in the control group of 2858 children who did not receive thrombolysis. Furthermore, 2 case reports describing IAT with tissue plasminogen activator (tPA) for occlusion of the frontoparietal trunk of the left MCA¹⁵ and thrombi located in the right MCA and anterior cerebral artery¹⁶ were not included. The reason for not including these

Table 1. IVT With tPA in 6 Childhood Strokes*

Author	Sex/Age, Years	Territory of Stroke	Cause of Stroke	Initial NIHSS Score	Latency Stroke-IVT	Outcome (Assessment)	Complication	Antithrombotic Treatment
Thirumilai ¹⁹	F/16	Left MCA	Cardiac embolism	10	105 minutes	No deficit (2 hours and hospital discharge)	0	Coumadin
Noser ²⁰	F/16	Right MCA	Paradoxical embolism	11	168 minutes	Near baseline functioning (2 months)	0	Warfarin, then PFO closure
Cannon ²¹	F/12	Right thalamus	Iatrogenic (cardiac embolism)	7	150 minutes	No deficit (24 hours and 6 months)	0	Aspirin 81 mg/day for 6 weeks
Carlson ²²	F/13	Right MCA	Unknown	10	<180 minutes	NIHSS 1, mRS 1 (5 months)	0	Warfarin
Shuyato ²³	M/16	Left MCA	Cardiac embolism	13	160 minutes	NIHSS 2-4, mRS 1 (8 hours and hospital discharge)	0	Unknown
Ortiz ²⁴	F/8	Left MCA	Unknown	22	120 minutes	mRS 3 (hospital discharge)	0	Aspirin

*tPA dose was 0.9 mg/kg body weight in all patients.
F indicates female; M, male; PFO, patent foramen ovale.

cases is that these children had no occlusion of sphenoidal or insular MCA, and to date, no CRT has investigated the safety and efficacy of IAT in more distally located MCA branch and anterior cerebral artery occlusion. Two additional case reports describing IAT with tPA for occlusion of MCA and IAT with urokinase for occlusion of BA were not included because time to treatment or the dose of the thrombolytic agent was not reported.^{17,18}

Included studies consisted of 2 children reported previously and 15 case reports from the literature describing a total 17 children who underwent IVT¹⁹⁻²⁴ (n=6; Table 1), IAT for MCA occlusion^{25,26} (n=3, Tables 2 and 3), IAT for BA occlusion^{10,27-30} (n=7; additional balloon angioplasty, n=3; Tables 4 and 5), and mechanical thrombolysis for BA occlusion³¹ (n=1).

IVT was performed in 6 children (5 girls; median age, 14 years; age range, 8 to 16 years) who presented with a median NIHSS score of 10 (range, 7 to 22) points.¹⁹⁻²⁴ All children underwent brain imaging and 5 children also cerebral angiography. The thrombolytic agent (tPA, 0.9 mg/kg body weight) was administered after a median delay of 150 minutes (range, 105 to 168 minutes) after the onset of stroke symptoms. No complication was reported. Clinical outcome was good in 4 patients (mRS 0, n=2; mRS 1, n=2), "near baseline functioning" after 2 months in one patient, and a mRS of 3 after 3 weeks in the remaining patient.

IAT for MCA occlusion was performed in 3 boys (median age, 12 years; age range, 7 to 15 years) who presented with a median NIHSS score of 22 (range, 9 to 28) points.^{25,26} The

terminal (C1) ICA was also occluded in one patient, and the third patient had a carotid T occlusion. The children underwent IAT with urokinase (n=2) and tPA (n=1) after a median delay of 300 minutes (range, 120 to 345 minutes) after the onset of stroke symptoms. One patient developed an asymptomatic ICH. Clinical outcome included complete resolution of the neurological deficits in the patient with isolated MCA occlusion, an mRS of 3 after 2.5 months in the boy with occlusion of C1 ICA and MCA, and the boy with T occlusion died from a malignant MCA infarct.

IAT for BA occlusion was performed in 7 children (5 boys; median age, 9 years; age range, 6 to 18 years) who presented with a locked-in syndrome in 3 cases; the remaining 4 children showed impaired consciousness and focal neurological deficits.^{10,27-30} Cerebral MRI delineated acute infarcts in the vertebrobasilar territory in 5 patients. In one boy without pretreatment MRI, nonenhanced CT scan was normal. They underwent IAT with urokinase (median dose, 750 000 IU; range, 200 000 to 1 000 000 IU) in 5 cases and tPA in 2 cases after a median delay of 20 hours (range, 4 hours 50 minutes to 72 hours) after the onset of stroke symptoms. Additional balloon angioplasty was done in 3 cases. One patient developed a small asymptomatic pontine ICH. Clinical outcome included complete resolution of the neurological deficits in 4 patients after 1 to 12 months, minimal symptoms (mRS score 1) after 6 months in one child, a moderate deficit (mRS score 2) after 3 months in one patient, and a severe deficit (mRS score 4) assessed after 4 months in another patient.

Table 2. Clinical Characteristics, Antithrombotic Therapy, and Outcome of 3 Children Treated With IAT for MCA Occlusion

Author	Sex/Age, Years	Cause of Stroke	Initial NIHSS Score	Antithrombotic Treatment	Outcome (Assessment)
Gruber ²⁵	M/7	Iatrogenic (cardiac surgery)	9	Unknown	No deficit (hospital discharge)
Bourekas ²⁶	M/15	Unknown	28	Oral aspirin 325 mg/day	NIHSS 8, mRS 3 (2.5 months)
Case 1	M/12	Unknown	22	Intravenous aspirin 250 mg/day	Death 2 days after symptom onset

F indicates female; M, male.

Table 3. Brain Imaging and Angiographic Findings and Complications of 3 Children Treated With IAT for MCA Occlusion

Author	Cerebral CT	Initial DSA (Brainstem Perforators)	Latency Stroke-IAT	Thrombolytic Agent	Balloon Angioplasty	Postinterventional DSA (Lenticulostriate Arteries)	Complication
Gruber ²⁵	No infarct	Right MCA occluded (not detected)	120 minutes	tPA (0.11 mg/kg=2.5 mg)	0	Complete recanalization (reappeared in 30 minutes)	0
Bourekas ²⁶	No infarct	Left C1-MCA occluded (not detected)	345 minutes	UK (560 000 IU)	0	C1 ICA recanalization, slow MCA flow (not detected)	Asymptomatic ICH
Case 1	Left MCA territory infarct	Carotid T occlusion	300 minutes	UK (750 000 IU)	0	ACA and ICA partial recanalization, MCA recanalization (not detected)	0

ACA indicates anterior cerebral artery.

Mechanical Thrombolysis for Basilar Artery Occlusion

A 16-year-old boy with locked-in syndrome underwent intra-arterial clot retrieval followed by balloon angioplasty 20 hours after symptom onset, and immediate recanalization was achieved. There was no complication and no neurological deficit on 3-month follow-up.

All Patients

In a total of 17 children (including our 2 cases) who underwent IVT (n=6) or IAT (n=10) or mechanical thrombolysis alone (n=1), 2 asymptomatic and no symptomatic ICH were observed. Sixteen children (94%) survived, and 12 (71%) had a good outcome (mRS score 0 or 1).

The probable and possible cause of stroke included cardiac and paradox embolism, spontaneous vertebral artery dissection, iatrogenic stroke, and stroke of unknown etiology. In contrast, no child with sickle cell disease, moyamoya disease,

transient cerebral arteriopathy of childhood, or postvaricella arteriopathy underwent thrombolysis.

Discussion

We found 17 case reports, including our own 2 patients, which described IVT with tPA in 6 (35%) children,^{19–24} IAT in 10 (59%) children, 3 with additional angioplasty,^{10,25–30} and mechanical thrombolysis alone for BA occlusion in one (6%) child.³¹ No symptomatic ICH was reported, but 2 asymptomatic ICHs occurred.

Six children with moderate to severe strokes underwent IVT with tPA in the 3-hour window using the same dose as in adults.^{19–24} No complication was reported, and 5 children had good outcomes (mRS score 0 to 1); the remaining child had an mRS score of 3 after 3 weeks. The low number of reported patients and the possibility of publication bias (children with a bad outcome may not have been reported)

Table 4. Clinical Characteristics, Antithrombotic Therapy, and Outcome of 7 Children Treated With IAT for BA Occlusion

Author	Sex/Age, Years	Cause of Stroke	Initial Deficit	Antithrombotic Treatment	Outcome (Assessment)
Cognard ¹⁰	M/8	Iatrogenic (cardiac surgery)	Unconscious, decerebrate rigidity	Full dose intravenous heparin 7 days	No deficit (3 months)
Rosman ²⁷	F/18	Atrial septal defect with left-to-right shunting	Locked-in syndrome	Oral anticoagulation for >2 years	mRS 4 (4 months)
Kirton ²⁸	M/15	Cryptogenic	Locked-in syndrome	Aspirin 81 mg/day (6 weeks)	No deficit (12 months)
Sungarian, Case 1 ²⁹	M/9	VA dissection after minor trauma	Impaired level of consciousness, dysarthria, right facial nerve palsy	Oral anticoagulation for 3 months, then aspirin for 1 year	No deficit (3 months)
Sungarian, Case 2 ²⁹	F/10	Bilateral VA dissection at C1–C2 location	Coma, left hemiparesis, and facial nerve palsy	Oral anticoagulation for 6 months, then aspirin for 1 year	No deficit (1 month)
Grigoriadis ³⁰	M/6	VA dissection (pars transversaria) after minor trauma	Locked-in syndrome	Oral anticoagulation for 6 months, then aspirin 75 mg/day	mRS 1 (6 months)
Case 2	M/9	Unknown	Impaired consciousness, tetraparesis, intermittent decerebrate rigidity	Intravenous aspirin 250 mg/day, then oral aspirin 100 MG	mRS 2 (3 months)

F indicates female; M, male; VA, vertebral artery.

Table 5. Brain Imaging and Angiographic Findings and Complications of 7 Children Treated With IAT for BA Occlusion

Author	Ischemic Infarcts at Cerebral MRI	Initial DSA (Brainstem Perforators)	Latency Stroke-IAT	Thrombolytic Agent	Balloon Angioplasty	Postinterventional DSA (Brainstem Perforators)	Complication
Cognard ¹⁰	Rt and lt pons, lt superior cerebellar peduncle, lt medial occipital lobe	BA occluded after trunk for PICA and AICA (not detected)	36 hours	UK (900 000 IU)	1	Partial recanalization (reappeared)	0
Rosman ²⁷	None	BA occlusion distal to AICA; BA—tip and both SCA filled from PCoA	72 hours	tPA (dose unknown)	0	Complete recanalization	0
Kirton ²⁸	Rt and lt pons	Mid-BA occluded, BA-tip filled from PCoA	20 hours	tPA (0.1 mg/kg)	1	Partial recanalization	0
Sungarian, Case 1 ²⁹	No MRI, nonenhanced cerebral CT normal	Mid-BA occluded, right VA dissection	6 hours	UK (750 000 IU)	0	Complete recanalization	0
Sungarian, Case 2 ²⁹	Pons	Mid-BA occluded, bilateral VA pseudoaneurysms at C1–C2 location	4 hours 50 Minutes	UK (1 000 000 IU)	0	Complete recanalization	Asymptomatic pontine hemorrhage
Grigoriadis ³⁰	Lt>rt pons	Mid-BA occluded, BA tip filled from PCoA (not detected)	44 hours	UK (200 000 IU)	1	Partial recanalization (reappeared)	0
Case 2	Lt thalamus, rt cerebellum, lt pons (subacute: lt cortical PCA territory, rt thalamus)	Midbasilar and distal BA occluded (not detected)	12 hours	UK (750 000 IU)	0	Partial recanalization (reappeared)	0

Rt indicates right; lt, left; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; AICA, anterior inferior cerebellar artery; SCA, superior cerebellar artery; PCoA, posterior communicating artery; VA, vertebral artery.

preclude any meaningful conclusion. Nevertheless, these data suggest that IVT may also be safe and effective in childhood stroke.

Childhood IAT for MCA occlusion was performed within 6 hours after the onset of symptoms in 3 children. All children except for one boy with carotid T occlusion treated with IAT survived. In adults, the Prolyse in Acute Cerebral Thromboembolism (PROACT) II study and the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) trial reported in 40% to 49% a favorable outcome (mRS 0 to 2) after IAT with pro-UK¹³ and UK³² for ischemic stroke due to MCA sphenoidal or insular occlusions and a 10% rate of symptomatic ICH.¹³ In MELT, 42% showed an excellent outcome (mRS 0 to 1). Due to the low number of reported children who underwent IAT for MCA occlusion, a meaningful comparison with the results of PROACT II and MELT is not feasible. However, the reported children suggest that revascularization of symptomatic MCA occlusion by means of IAT may be safe and effective in childhood. The lethal outcome of the boy who presented with a T occlusion and showed no MCA recanalization after IAT is in line with the unfavorable outcome of adults with this type of vessel occlusion.³³

Eight children underwent IAT in 7 cases (additional balloon angioplasty, n=3)^{10,27–30} or intra-arterial clot retrieval followed by balloon angioplasty (n=1)³¹ for BA occlusion. All children survived, 6 with no or minimal deficits (mRS 0 to 1), one with a mRS of 2, and one remained severely disabled (mRS 4) after a follow-up ranging between 1 and 12 months. In adults, no large CRT has investigated thrombolysis in BA occlusion, and all patients were reported in retrospective case series. The majority of adult patients with this disease

remained disabled and died after IAT or IVT, and a favorable outcomes (mRS 0 to 2) occurred in 21% to 35%.^{34,35} The results of the children treated with IAT after BA occlusion analyzed in this review compare well with those of adults undergoing the same treatment, but the comparison is limited due to the drawbacks mentioned. In a few children, the doses of tPA and UK were lower compared with those administered in adults; however, several children received adult dosing without hemorrhagic complications.^{11,32}

It is surprising that IAT was used as often as IVT in children, although most patients with adult stroke are treated with IVT. Furthermore, most stroke centers have more experience with IVT. A possible explanation is that most children with stroke are admitted after the 3-hour time window. This delay of diagnosing childhood stroke may be explained by low public and physician awareness, difficulties in taking a patient's history, and the diagnostic challenge due to stroke mimics and associated symptoms such as epileptic seizures.

Four children underwent balloon angioplasty in addition to IAT (n=3) or intra-arterial clot retrieval (n=1) without any complication,^{10,28,30,31} which indicates that mechanical thrombolysis is also a treatment option in carefully selected children with ischemic stroke. The ongoing growth and the small diameter of the cerebral arteries in childhood suggest that stents are not indicated and appropriately designed catheters are needed. It is noteworthy that the actual American Heart Association guidelines for the early management of adults with ischemic stroke recommend that (1) the Mechanical Embolus Removal in Cerebral Embolism (MERC) retriever,³⁶ which is the only yet US Food and Drug Administration-approved mechanical thrombolytic treatment,

should be studied in additional clinical trials; and (2) other mechanical endovascular treatments should be used in the setting of clinical trials.³⁷ Thus, mechanical thrombolysis has been successfully used in addition to IAT or as the only endovascular therapy, but this treatment should be performed by experienced interventionalists in carefully selected patients included in CRTs.

The cause of stroke in children who underwent thrombolytic treatment included cardiac and paradox embolism, spontaneous vertebral artery dissection, iatrogenic stroke, and stroke of unknown etiology. In contrast, no child with sickle cell disease, moyamoya disease, transient cerebral arteriopathy, or postvaricella arteriopathy, which are important causes of pediatric stroke, underwent thrombolysis.

The major limitation of this review is the small sample size and the potential of publication bias because children with a bad outcome, including symptomatic ICH after thrombolytic treatment, may not have been reported. However, the retrospective study of Janjua et al on children who underwent IVT or IAT and were entered in the US Nationwide Inpatient Sample reported no symptomatic ICH in 46 children.⁸ Another drawback of this review is that important data were not given in all reports, in particular the severity of the neurological deficit at presentation and after 3 months, were not quantified with a stroke scale in all children.

In conclusion, the knowledge about thrombolysis in childhood stroke is limited. The reported outcomes of children with stroke who underwent thrombolysis suggest that this treatment may also be beneficial in pediatric patients and that children should have access to specialized stroke centers performing thrombolysis. However, there is a need for CRT to determine the appropriate dosage, safety, and efficacy of thrombolysis in children with acute stroke.

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None.

References

- Broderick J, Talbot GT, Prenger E, Leach A, Brott T. Stroke in children within a major metropolitan area: the surprising importance of intracerebral hemorrhage. *J Child Neurol*. 1993;8:250–255.
- Schoenberg BS, Mellinger JF, Schoenberg DG. Cerebrovascular disease in infants and children: a study of incidence, clinical features, and survival. *Neurology*. 1978;28:763–768.
- Giroud M, Lemesle M, Gouyon JB, Nivelon JL, Milan C, Dumas R. Cerebrovascular disease in children under 16 years of age in the city of Dijon, France: a study of incidence and clinical features from 1985 to 1993. *J Clin Epidemiol*. 1995;48:1343–1348.
- Lynch JK, Hirtz DG, DeVeber G, Nelson KB. Report of the national institute of neurological disorders and stroke workshop on perinatal and childhood stroke. *Pediatrics*. 2002;109:116–123.
- Lanthier S, Carmant L, David M, Larbrisseau A, de Veber G. Stroke in children: the coexistence of multiple risk factors predicts poor outcome. *Neurology*. 2000;54:44–47.
- deVeber G, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *J Child Neurol*. 2000;15:316–324.
- Pavlovic J, Kaufmann F, Boltshauser E, Capone Mori A, Gubser Mercati D, Haenggeli C, Keller E, Lüttsch J, Maroz J, Ramelli G, Roulet Perez E, Schmitt-Mechelke T, Weissert M, Steinlin M. Neuropsychological problems after paediatric stroke: two year follow-up of Swiss children. *Neuropediatrics*. 2006;37:13–19.
- Janjua N, Nasar A, Lynch JK, Qureshi AI. Thrombolysis for ischemic stroke in children: data from the nationwide inpatient sample. *Stroke*. 2007;38:1850–1854.
- Keidan I, Shahar E, Barzilay Z, Passwell J, Brand N. Predictors of outcome of stroke in infants and children based on clinical data and radiologic correlates. *Acta Paediatr*. 1994;83:762–765.
- Cognard C, Weill A, Lindgren S, Piotin M, Castaings L, Moret J. Basilar artery occlusion in a child: ‘clot angioplasty’ followed by thrombolysis. *Childs Nerv Syst*. 2000;16:496–500.
- The National Institute of Neurological Disorders and Stroke rt-PA Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
- The ATLANTIS ECASS and NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363:768–774.
- Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, Silver F, Rivera F, for the PROACT Investigators. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *JAMA*. 1999;282:2003–2011.
- Saver JL. Intra-arterial fibrinolysis for acute ischemic stroke. The message of MELT. *Stroke*. 2007;38:2627–2628.
- Golomb MR, Rafay M, Armstrong D, Massicotte P, Curtis R, Hune S, deVeber GA. Intra-arterial tissue plasminogen activator for thrombosis complicating cerebral angiography in a 17-year-old girl. *J Child Neurol*. 2003;18:420–423.
- Benedict SL, Ni OK, Schloesser P, White KS, Bale JF Jr. Intra-arterial thrombolysis in a 2-year-old with cardioembolic stroke. *J Child Neurol*. 2007;22:225–227.
- Yoshikawa H. Basilar artery infarction. *Arch Dis Child*. 2005;90:410.
- Losourdo G, Giacchino R, Castagnola E, Gattorno M, Costabel S, Rossi A, Amato S, Di Pietro P, Molinari AC. Cerebrovascular disease and varicella in children. *Brain Dev*. 2006;28:366–370.
- Thirumalai SS, Shubin RA. Successful treatment for stroke in a child using recombinant tissue plasminogen activator. *J Child Neurol*. 2000;15:558.
- Noser EA, Felberg RA, Alexandrov AV. Thrombolytic therapy in an adolescent ischemic stroke. *J Child Neurol*. 2001;16:286–288.
- Cannon BC, Kertesz NJ, Friedman RA, Fenrich AL. Use of tissue plasminogen activator in a stroke after radiofrequency ablation of a left-sided accessory pathway. *J Cardiovasc Electrophysiol*. 2001;12:723–725.
- Carlson MD, Leber S, Deveikis J, Silverstein FS. Successful use of rt-PA in pediatric stroke. *Neurology*. 2001;57:157–158.
- Shuayto MI, Lopez JI, Greiner F. Administration of intravenous tissue plasminogen activator in a pediatric patient with acute ischemic stroke. *J Child Neurol*. 2006;21:604–606.
- Ortiz GA, Koch S, Wallace DM, Lopez-Alberola R. Successful intravenous thrombolysis for acute stroke in a child. *J Child Neurol*. 2007;22:749–752.
- Gruber A, Nasel C, Lang W, Kitzmüller E, Bavinski G, Czech T. Intra-arterial thrombolysis for the treatment of perioperative childhood cardioembolic stroke. *Neurology*. 2000;54:1684–1686.
- Bourekas EC, Slivka AP, Casavant MJ. Intra-arterial thrombolysis of a distal internal carotid artery occlusion in an adolescent. *Neurocrit Care*. 2005;2:179–182.
- Rosman NP, Adhami S, Mannheim GB, Katz NP, Klucznik RP, Muriello MA. Basilar artery occlusion in children: misleading presentations, ‘locked-in’ state, and diagnostic importance of accompanying vertebral artery occlusion. *J Child Neurol*. 2003;18:450–462.
- Kirtan A, Wong JH, Mah J, Ross BC, Kennedy J, Bell K, Hill MD. Successful endovascular therapy for acute basilar thrombosis in an adolescent. *Pediatr*. 2003;112:e248–e251.
- Sungarian A, Duncan JA. Vertebrobasilar thrombosis in children: report of two cases and recommendations for treatment. *Pediatr Neurosurg*. 2003;38:16–20.
- Grigoriadis S, Gomori JM, Grigoriadis N, Cohen JE. Clinically successful late recanalization of basilar artery occlusion in childhood: what are the odds? Case report and review of the literature. *J Neurol Sci*. 2007;260:256–260.

31. Zaidat OO, Tolbert M, Smith TP, Alexander MJ. Primary endovascular therapy with clot retrieval and balloon angioplasty for acute basilar artery occlusion. *Pediatr Neurosurg.* 2005;41:323–327.
32. Ogawa A, Mori E, Minematsu K, Taki W, Takahashi A, Nemoto S, Miyamoto S, Sasaki M, Inoue T, for The MELT Japan Study Group. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke. The Middle cerebral artery Embolism Local fibrinolytic intervention Trial (MELT) Japan. *Stroke.* 2007;38:2633–2639.
33. Arnold M, Nedeltchev K, Mattle HP, Loher TJ, Stepper F, Schroth G, Brekenfeld C, Sturzenegger M, Remonda L. Intra-arterial thrombolysis in 24 consecutive patients with internal carotid artery t occlusions. *J Neurol Neurosurg Psychiatry.* 2003;74:739–742.
34. Arnold M, Nedeltchev K, Baumgartner RW, Remonda L, Schroth G, Loher TJ, Stepper F, Sturzenegger M, Schuknecht B, Mattle HP. Clinical and radiological predictors of recanalization and outcome in 40 patients with acute basilar artery occlusion treated with intra-arterial thrombolysis. *J Neurol Neurosurg Psychiatry.* 2004;74:857–862.
35. Lindsberg PJ, Mattle HP. Therapy of basilar artery occlusion: a systematic analysis comparing intra-arterial and intravenous thrombolysis. *Stroke.* 2006;37:922–928.
36. Flint AC, Duckwiler GR, Budzik RF, Liebeskind DS, Smith WS; MERCI and Multi MERCI Writing Committee. Mechanical thrombectomy of intracranial internal carotid occlusion: pooled results of the MERCI and Multi MERCI Part I trials. *Stroke.* 2007;38:1274–1280.
37. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EFM. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association, Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the atherosclerotic peripheral vascular disease and quality of care outcomes in research interdisciplinary working groups. *Circulation.* 2007;115:478–534.