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. It has an incidence of 2.5 to 13 per 100,000 children per year and is more common in males and blacks. 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. 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. Furthermore, mortality in childhood stroke ranges from 7% to 28%. Controlled, randomized trials (CRT) and meta-analyses have proven the efficacy of intravenous thrombolysis (IVT) and intra-arterial thrombolysis (IAT) 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...
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, hemihyphsthesia, 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 performed 3 hours after symptom onset revealed 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. Transthoracal 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%]). 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. Furthermore, risk factors and potential stroke etiologies were not reported for most of the 46 children. 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 MCA and thrombi located in the right MCA and anterior cerebral artery were not included. The reason for not including these
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 occlusion25,26 (n = 3, Tables 2 and 3 ), IAT for BA occlusion25,26 (n = 7; 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Sex/Age, Years</th>
<th>Cause of Stroke</th>
<th>Initial NIHSS Score</th>
<th>Antithrombotic Treatment</th>
<th>Outcome (Assessment)</th>
<th>Antithrombotic Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruber25</td>
<td>M/7</td>
<td>iatrogenic (cardiac surgery)</td>
<td>9</td>
<td>Unknown</td>
<td>No deficit (hospital discharge)</td>
<td>No deficit (hospital discharge)</td>
</tr>
<tr>
<td>Bourkeas26</td>
<td>M/15</td>
<td>Unknown</td>
<td>28</td>
<td>Oral aspirin 325 mg/day</td>
<td>NIHSS 8, mRS 3 (2.5 months)</td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>M/12</td>
<td>Unknown</td>
<td>22</td>
<td>Intravenous aspirin 250 mg/day</td>
<td>Death 2 days after symptom onset</td>
<td></td>
</tr>
</tbody>
</table>

F indicates female; M, male.
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>
<thead>
<tr>
<th>Author</th>
<th>Sex/Age, Years</th>
<th>Cause of Stroke</th>
<th>Initial Deficit</th>
<th>Antithrombotic Treatment</th>
<th>Outcome (Assessment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognard10</td>
<td>M/8</td>
<td>Iatrogenic (cardiac surgery)</td>
<td>Unconscious, decerebrate rigidity</td>
<td>Full dose intravenous heparin 7 days</td>
<td>No deficit (3 months)</td>
</tr>
<tr>
<td>Rosman27</td>
<td>F/18</td>
<td>Atrial septal defect with left-to-right shunting</td>
<td>Locked-in syndrome</td>
<td>Oral anticoagulation for 3 months, then aspirin for 1 year</td>
<td>mRS 4 (4 months)</td>
</tr>
<tr>
<td>Kirton28</td>
<td>M/15</td>
<td>Cryptogenic</td>
<td>Locked-in syndrome</td>
<td>Aspirin 81 mg/day (6 weeks)</td>
<td>No deficit (12 months)</td>
</tr>
<tr>
<td>Sungarian, Case 129</td>
<td>M/9</td>
<td>VA dissection after minor trauma</td>
<td>Impaired level of consciousness dysarthria, right facial nerve palsy</td>
<td>Oral anticoagulation for 6 months, then aspirin for 1 year</td>
<td>No deficit (3 months)</td>
</tr>
<tr>
<td>Sungarian, Case 229</td>
<td>F/10</td>
<td>Bilateral VA dissection at C1–C2 location</td>
<td>Coma, left hemiparesis, and facial nerve palsy</td>
<td>Oral anticoagulation for 75 mg/day</td>
<td>mRS 1 (6 months)</td>
</tr>
<tr>
<td>Grigoriadis30</td>
<td>M/6</td>
<td>VA dissection (pars transversaria) after minor trauma</td>
<td>Locked-in syndrome</td>
<td>Intravenous aspirin 250 mg/day, then oral aspirin 100 MG</td>
<td>mRS 2 (3 months)</td>
</tr>
<tr>
<td>Case 2</td>
<td>M/9</td>
<td>Unknown</td>
<td>Impaired consciousness, tetraparesis, intermittent decerebrate rigidity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery.
Table 5. Brain Imaging and Angiographic Findings and Complications of 7 Children Treated With IAT for BA Occlusion

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

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

Eight children underwent IAT in 7 cases (additional balloon angioplasty, n=3) or intra-arterial clot retrieval followed by balloon angioplasty (n=1) 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%. 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. 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 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, 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 (MERCi) retriever, 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. 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 interventionists 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. 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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Disclosures

None.

References


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