View Point

# Acute Ischemic Stroke in Children – Should We Thrombolyze?

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## Abstract

Ischemic stroke is a major cause of acute neurological symptoms in children with significant long-term neurological sequelae. Unlike in the adult population, the clinical presentation of strokes in children may not be stereotyped. Hence, many other differential diagnostic possibilities might have to be considered in the emergency setting. Due to this heterogeneous presentation and the resultant clinical dilemma in the early detection, acute thrombolysis even now remains as a very rarely tried therapeutic option in children. Many case reports over these years have shown consistently good results of acute intravenous thrombolysis in children with tissue plasminogen activator (tPA) administered within the time frame. There are also some recent reports of endovascular interventions. However, unlike in the adult population, class 1 clinical studies and good Randomized controlled *trials* (RCT) are yet to emerge in children. The absence of age-appropriate safety and outcome data for the commonly used thrombolytic agents in children is another major roadblock for developing clinical guidelines and recommendations for this age group. The ambitious Thrombolysis in Pediatric Stroke (TIPS) trial had to be terminated prematurely due to poor patient enrolment. This review critically looks at the current status of the acute management of ischemic strokes in children with a specific emphasis on thrombolytic therapy. Until we have better evidence-based guidelines for this age group, it will be prudent to develop robust institutional pathways to provide this important intervention for all eligible children with acute strokes.

**Keywords:** COVID-19, pediatric stroke, thrombolysis, Tissue plasminogen activator (tPA)

Ischemic stroke is an important acute neurological disorder in children with an annual incidence ranging from 1 to 2 per 100,000 children.[1] The consequences of the brain injury remain throughout the life cycle contributing to an overall higher prevalence of neurological disabilities. More than fifty percent of children who had an episode of acute ischemic stroke proceed to have long-lasting motor deficits as a consequence.[2] Due to the heterogeneous presentation and the resultant clinical dilemma in the early detection, acute thrombolysis even now remains a very rarely tried therapeutic option in children. This review critically looks at the current status of acute stroke care in children with a specific emphasis on thrombolytic therapy.

## Barriers to care for children with acute stroke

Stroke is primarily considered as a neurological disorder of the elderly. An acute focal neurological deficit in the adult is usually thought to be of vascular origin unless there are other strong pointers for an alternate etiological possibility. However, ischemic stroke traditionally comes much lower in the list of etiological possibilities in children presenting with an acute focal neurological deficit. As a result, pertinent evaluation gets inordinately delayed, and the child gets out of the therapeutic window for acute interventions. The clinical presentation of acute stroke in children is also not as stereotyped as in the adult population and to a great extent depends on the age of occurrence. Childhood strokes may further be subdivided into three groups: perinatal stroke, stroke in infancy and early childhood and adolescent stroke. The symptoms will be more nonspecific in younger children. Perinatal stroke presents usually with focal seizures or lethargy in the first few days after birth. Infants may also present similarly with deterioration in their general condition, increased crying and irritability, sleepiness, feeding difficulty, vomiting, sepsis-like symptoms, or seizures. Older children and adolescents present more like adults. Hemiparesis is the most common focal manifestation, occurring in up to 94% of children in this group. Posterior circulation strokes have more frequent seizures, posturing, and nonspecific symptoms along with ataxia, visual symptoms in children.[3] Hemorrhagic strokes most commonly present as headaches or altered levels of consciousness and are more likely to cause vomiting than acute ischemic strokes.[4]

## Emergency management of acute ischemic strokes in children

There are several challenges in preparing a center for the emergency management of stroke in children, including the infrequency of childhood strokes, the lack of evidence-based data for developing protocols for emergency management, and

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**Submitted:** 08-Jun-2021 **Revised:** 25-Jul-2021 **Accepted:** 25-Aug-2021
**Published:** 22-Oct-2021



**DOI:** 10.4103/aian.aian_527_21

the lack of physician as well as community awareness about strokes in children.

Early treatment decisions to maintain optimal fluid, electrolyte and glucose levels, treatment of hyperthermia, and antithrombotic management may be more pragnatic in improving the current outcomes as the majority of children with ischemic strokes still do not present or get identified in time for acute interventions.[5] Even when emergency revascularization therapies are not appropriate, proper etiologic diagnosis and supportive care, along with strategies for prevention of stroke recurrence are invaluable steps for improving the outcomes and prognosis. An institutional stroke pathway should be made available in all centers dealing with acute pediatric strokes.

## Brain imaging – CT or MRI?

The probability of ischemic and/or hemorrhagic stroke is high in adults presenting with an acute focal neurological deficit. However, the probability of stroke in children is much lower, making a positive confirmation of stroke and/or vessel occlusion imperative in most instances for planning any revascularization strategies. In one recent series, stroke was the fourth most common cause of acute childhood focal neurological deficit, being less common than hemiplegic migraine, seizures, and Bell's palsy.[6] MRI (DWI, GRE, MRA images) rather than non-contrast computed tomography (NCCT) is, therefore, a more useful initial imaging option in children with stroke-like symptoms. However, MR imaging in children is time-consuming and as a result, the option of MRI as the initial imaging option greatly limits the chances for successful revascularization in the window period. It will be prudent to follow the adult protocols in adolescents and proceed with a CT scan as the initial imaging option if the patient presents within the window period with the classical focal neurological deficits. However, younger children in whom the presentation is atypical should better undergo ultra-fast MR imaging protocols with 3D Time of Flight (TOF) angiography to establish the diagnosis. However, the limitations of TOF imaging in the estimation of the extent of vessel occlusion should be considered during the clinical decision making for thrombolysis. There is a chance of critical stenosis being interpreted as total occlusion in view of the dependency of this technique on the arterial blood flow.

## Can ischemic strokes in children be thrombolysed?

Thrombolytic therapy is a well-established antithrombotic modality with acute ischemic strokes in adults. The goal of thrombolytic therapy is clot lysis and the rapid restoration of normal blood flow. As per the pivotal studies, thrombolysis with tPA must be initiated within 4.5 h of symptom onset to maintain a favorable risk-benefit ratio. At present, tPA administration is not approved for children with ischemic strokes outside the clinical research settings. However, tPA is routinely being used for clot lysis in children with both arterial and venous thrombosis for various non-neurological disorders.[7-9] Many case reports and clinical series in children from neonate to adolescent age group have shown good results for the clearance of obstructed catheters as well as in thrombotic disorders of aorta, renal arteries and great veins. However, the absence of evidence-based data on age-appropriate safety and efficacy of tPA is the major roadblock for the development of best clinical practice guidelines for the usage of tPA in children with ischemic strokes. The fibrinolytic system in children is not mature and has lower levels of endogenous tPA and higher levels of plasminogen activator inhibitor 1 (PAI-1).[10] Moreover, increased volume of distribution and more rapid hepatic clearance suggest that children will clear tPA more quickly from their system. This raises the possibility that a higher proportionate dose of tPA would be required for thrombolysis as compared to adults. This should be weighed against the chances of major bleeding. However, the rarity of leukoaraiosis in children might act as a major protective factor against large intracerebral hemorrhage after tPA administration.

Currently, information regarding intravenous tissue plasminogen activator (tPA) administration for strokes in children consists of case reports, small case series, and hospital database documentation. There is an urgent need for developing robust evidence through good clinical trials on acute thrombolysis for ischemic stroke in children. Alshekhlee *et al*.[11] analyzed the Kids' Inpatient Database over 11 years and found that only 0.7% of the children with ischemic strokes received tPA. Delay in stroke diagnosis, the unfamiliarity of many pediatric centers with the administration of tPA, and the off-label status of tPA in childhood stroke were considered to be the major factors contributing to this low rate.

In 2010, the National Institute of Neurological Disorders and Stroke (NINDS) funded the Thrombolysis in Pediatric Stroke (TIPS) trial to prospectively investigate the safety, best therapeutic dose, and feasibility of treatment with intravenous tPA in children with ischemic stroke.[12] This open-label, prospective, 5-year multicenter international safety and dose-finding study was designed to determine the maximal safe dose of intravenous tPA (0.75, 0.9, or 1.0 mg/kg) for children aged 2 to 17 years within 4.5 h from symptom onset. To reduce the inclusion of stroke mimics, the trial protocol mandated the positive imaging confirmation of the ischemic stroke and vessel occlusion by either MRI/MRA or NCCT/CT angiography for the inclusion into the trial. This was a major deviation from the established adult protocols which clearly restricted the inclusion of eligible patients within the therapeutic window. A total of 93 children aged 2 to 17 years were screened for inclusion in TIPS. Only 46% (43/93) of the children screened for a possible acute stroke confirmed to have an ischemic stroke. The remainder (50/93 or 54%) had stroke mimics. Among children with confirmed stroke, 21 had a medical contraindication to receive tPA. Two patients were excluded because of lack of occlusion on arterial imaging. Ten were outside the treatment window but presented within 12 h, and ≥7 of these presented within approximately 5 h. One arrived 3.5 h after documented onset of symptoms but failed anesthesia, and one missed the window by 15 min because of a delay at the scanner. Six children were excluded

as the Pediatric version of the NIH stroke scale (PedNIHSS) score was below the study cut-off of 6, before a revision downward of the PedNIHSS to ≥4 for patient inclusion in TIPS. Ultimately, only 1 out of 93 screened children was enrolled in the study, which was significantly lower than the expected rate. Subsequently, this ambitious trial was terminated by NINDS in December 2013 citing poor patient enrolment. The failure of this trial was mainly attributed to the lack of dedicated pediatric stroke services in many of the proposed centers.

However, in a *post hoc* analysis, TIPS investigators have shown that the development of better acute management facilities and stroke units is a direct result of this trial. This study also brought out the need for special expertise in the clinical diagnosis and management of acute focal neurological deficits in children. More than 50% of the screened subjects in TIPS had a stroke mimic, which was much higher compared to the adult population. All the pediatric stroke teams should be aware of this possibility, before making decisions on the management of acute thrombolysis in children.

The premature termination of the TIPS trial was a major setback to the efforts of developing evidence-based therapeutic protocols and guidelines for acute revascularization therapies in children with ischemic strokes . Marecos *et al*.[13] subsequently reported a retrospective 5-year audit on the eligibility for thrombolytic therapy in a tertiary center in the UK. The aim was to define local criteria for children with hyperacute ischemic strokes who might benefit from thrombolysis, to examine how many would have met these criteria, and to describe the barriers to hyperacute treatment in childhood ischemic strokes. Of the 107 children with acute ischemic strokes, they found that none would have qualified for thrombolytic therapy based on their criteria, though three (2.8%) would have qualified if the transfer had been timely. The major barriers to thrombolysis were delayed diagnosis, delayed transfer to the tertiary stroke center, and medical co-morbidities. This study showed that 39% of the patients were excluded due to the delay in diagnosis, clearly highlighting the need for better awareness among primary care physicians, pediatricians, and the community at large regarding acute stroke interventions.

Stroke in the adolescent age group needs special mention as many of them will be potential candidates for recanalization therapy. In a recent retrospective study of acute ischemic stroke in adolescents (10 to 18 years), Rambaud *et al*.[14] reported that 17% underwent IV thrombolysis, 12% endovascular therapy, and only 1 subject had an asymptomatic hemorrhagic transformation. They highlighted that this cohort represented a specific subgroup sharing both pediatric and adult characteristics. Recently, it has been demonstrated that tenecteplase, a fibrin-specific thrombolytic agent, is equally efficacious or better in opening the arteries and not inferior to alteplase in clinical outcomes in adult patients.[15] With a relatively shorter administration time, the use of tenecteplase might be more prudent in the pandemic and probably might reduce the chances for viral transmission in the emergencies.[16] However, studies specifically in children are yet to emerge.

### Endovascular options

Endovascular options for treating acute ischemic stroke have significantly advanced in the last decade in the adult population. However, to date, there are no published guidelines, clinical trials, or prospective studies investigating acute endovascular intervention strategies in children. The evidence on mechanical thrombectomy in children consists of case reports and small case series, which might possibly have a publication bias. The safety of mechanical thrombectomy in children is currently undetermined. In adults, documented complications of mechanical thrombectomy for ischemic strokes include vasospasm, dissection, vessel perforation and new territory embolization.[17] There are multiple case reports[18-20] on mechanical thrombectomy in children. However, most of the current pediatric stroke treatment protocols advise against mechanical thrombectomy outside the clinical research settings, pending sufficient data to support its safety and efficacy in children.[21] In a retrospective multicentric review of pediatric stroke patients aged 1 month to 16 years, 8 patients had undergone mechanical thrombectomy for acute ischemic stroke with large vessel occlusion. Thromboysis In Cerebral Infarction score 3 (TICI) flow of 67.3% was achieved with either intraarterial (IA) thrombolysis or mechanical thrombectomy. Mechanical thrombectomy group showed significantly better clinical (79.5% versus 20.5%; $P = 0.001$) and radiographic outcomes (complete recanalization, 79.1% versus 38.9%; $P = 0.002$) with fewer complications (13.6% versus 37.5%; $P = 0.006$) than the IA fibrinolytic group. Overall, it can be concluded that endovascular recanalization treatment is feasible and seems to be relatively safe in childhood strokes with large vessel occlusion. Larger studies are needed to properly assess the efficacy and risks of endovascular therapy in pediatric strokes.[22]

### Special considerations during the COVID-19 pandemic

The causative association between COVID-19 infection and stroke is still debatable.[23-25] Nonetheless, the global COVID-19 stroke registry through a multicentric study concluded that COVID-associated strokes might be more severe with higher mortality rates and poorer functional outcomes compared to non-COVID strokes.[26] Multiple case reports regarding stroke in children associated with COVID-19 are being published worldwide.[27-30] Along with the propensity of SARS-CoV-2 infection to cause a prothrombotic state, the increase in sedentary life habits due to the pandemic restrictions might also act as a predisposing factor in some of these children.

## Conclusions and a Pragmatic Approach

Evidence-based medicine from large-scale stroke trials that guide stroke therapy in adult patients does not exist for children with stroke. This status is unlikely to change in the near future. Early identification and immediate management of childhood stroke require the development of dedicated stroke services

with sufficient expertise and involvement of interdisciplinary teams. Dedicated stroke units established for adults provide an example of this multidisciplinary approach that might be replicated for the evaluation and treatment of pediatric strokes. The organizational infrastructure of these centers may be adapted for the treatment of children.

As per the available recommendations, tPA may be offered to childhood ischemic strokes strictly in the recommended window period and in a center familiar and well experienced with both adult and pediatric protocols for thrombolysis, preferably as part of an ongoing clinical research initiative. However, it will be better to develop a pragmatic approach in dealing with children with acute ischemic strokes based on the age at occurrence and comorbidities, rather than considering the pediatric population as a monolithic group. Children with a previous diagnosis of cardiac or hematologic disorders with a higher chance for thromboembolic events and ischemic strokes should be identified from the database, triaged faster in emergencies, and the initial evaluation should be fast-tracked irrespective of age.

Adolescents presenting initially with acute focal neurological deficits suggestive of ischemic strokes should be considered as potentially eligible for thrombolysis and should be prioritized for thrombolytic therapy as in adult stroke protocols in view of the relative rarity of stroke mimics in this population. Established workflow for the adult strokes should be employed faster to minimize the time delay. Younger children with suspected stroke/stroke mimics should definitely undergo an MRI brain and MR angiography to positively establish the diagnosis of an acute vascular event before any therapeutic intervention. It will be prudent to immediately refer all the older school-going children presenting with acute focal neurological deficits suggestive of ischemic strokes to a center well versed in the care of pediatric and adult patients with acute strokes. They should be actively screened for a possible acute vascular event, considering the option of thrombolysis in eligible patients. Children aged 1–18 years with large vessel occlusion with salvageable penumbra may be referred for thrombectomy within 24 h as per current guidelines, given the excellent outcome in adult clinical trials.[31] Till we get further evidence-based data, such an approach will enhance the chances of successful thrombolysis in eligible children. This might also reduce the chances for inappropriate thrombolysis and the associated risks in younger children with strokes and stroke mimics. A detailed analysis of all the current evidence for each these clinical scenarios is beyond the scope of this review. Readers are advised to go through the updated clinical consensus documents for more information.[32]

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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