

Bacterial endocarditis in a child presenting with acute arterial ischemic stroke: should thrombolytic therapy be absolutely contraindicated?

MARILYN TAN MD¹ | DEREK ARMSTRONG MD² | CATHERINE BIRKEN MD³ | ARI BITNUN MD⁴ |
CHRISTOPHER A CALDARONE MD⁵ | PETER COX MB CHB⁶ | WALTER KAHR MD PHD⁷ |
DAUNE MACGREGOR MD¹ | RAND ASKALAN PHD MD^{1,8}

1 Department of Pediatrics, Hospital for Sick Children, Toronto, Canada. **2** Department of Diagnostic Imaging, Hospital for Sick Children, Toronto, Canada. **3** Pediatric Medicine, Hospital for Sick Children, Toronto, Canada. **4** Division of Infectious Diseases, Hospital for Sick Children, Toronto, Canada. **5** Heart Center – Cardiovascular Surgery, Hospital for Sick Children, Toronto, Canada. **6** Department of Pediatric Critical Care, Hospital for Sick Children, Toronto, Canada. **7** Division of Hematology/Oncology, Hospital for Sick Children, Toronto, Canada. **8** Division of Neurology, Hospital for Sick Children, Toronto, Canada.

Correspondence to Dr Rand Askalan at Division of Neurology, Hospital for Sick Children, 555 University Avenue, Toronto, ON, Canada M5G 1X8.
E-mail: r.askalan@utoronto.ca

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LIST OF ABBREVIATIONS

IE	Infective endocarditis
MRA	Magnetic resonance angiography
NIHSS	National Institutes of Health stroke scale
tPA	Tissue plasminogen activator

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Thrombolysis is considered to be contraindicated in acute ischemic stroke secondary to infective endocarditis (IE). We report a 12-year-old female who presented with acute dense right hemiparesis and aphasia. Cranial magnetic resonance imaging and angiography showed multiple diffusion-restricted lesions in the left hemisphere and absence of flow in the left internal carotid artery. She was treated with intra-arterial tissue plasminogen activator within 6 hours of her presentation. Subsequently she was diagnosed with pneumococcal endocarditis and underwent debridement of vegetations and patch repair of the mitral valve. The patient did not have hemorrhagic complications following thrombolytic therapy or surgery. Pathological analysis of the mitral valve vegetations revealed mostly fibrin thrombus. Follow-up imaging showed complete recanalization of the left internal carotid artery, and the patient had a remarkable neurological recovery. This is the first case report of successful intra-arterial thrombolytic therapy in childhood IE-related stroke. We believe that thrombolytic therapy contributed to a favorable outcome in our patient and may be safe in selected patients with childhood IE-related acute ischemic stroke.

Thrombolytic therapy is a well established therapy and standard of care in adults with acute ischemic stroke.^{1,2} In children, however, literature on thrombolytic therapy is limited to a few case reports and series.^{3,4} Guidelines on the use of thrombolytic agents for childhood acute ischemic stroke are mainly extrapolated from adult-based guidelines.

In adult acute ischemic stroke, infective endocarditis (IE) is considered an absolute contraindication for thrombolytic therapy. This is because of the increased risk of intracranial hemorrhage and the general perception that stroke, in this setting, is caused by septic rather than thrombotic emboli. To our knowledge, this is the first reported case of successful intra-arterial thrombolytic ther-

apy in childhood arterial ischemic stroke secondary to bacterial endocarditis. The authors have written consent from the patient's parents to publish this case.

CASE REPORT

A 12-year-old previously healthy right-handed female was admitted to our institution for fever of unknown origin. She had a 12-day history of fever, anorexia, and muscle aches, despite a 5-day course of azithromycin started 10 days before presentation. Past medical, family, personal, and social histories were unremarkable. Routine childhood immunizations were up to date.

Her systemic physical examination was unremarkable, including absence of murmur, Osler nodes, Janeway

lesions, Roth spots, and conjunctival or splinter hemorrhages. Initial laboratory investigations revealed a hemoglobin of 108g/L, a white blood cell count of $14.6 \times 10^9/L$, a platelet count of $544 \times 10^9/L$, normal electrolytes, normal liver and renal function tests, and normal international normalized ratio and partial thromboplastin time. Erythrocyte sedimentation rate and C-reactive protein were elevated. Chest radiography was normal.

On the second hospital day, the first of three blood culture sets was reported positive for gram-positive cocci in pairs and chains; intravenous ceftriaxone and vancomycin were commenced. Later that day the patient presented with sudden onset of confusion and right hemiparesis including the face. The patient had normal vital signs and was afebrile at that time. Neurological examination revealed a drowsy, aphasic patient who did not follow commands. She had right-sided central cranial nerve VII palsy, right-sided dense hemiplegia with flaccid tone, and right Babinski sign. Her National Institutes of Health stroke scale (NIHSS) score was 18. Acute cranial magnetic resonance imaging (MRI) revealed multiple diffusion-restricted lesions in the left hemisphere, including the uncus, putamen, posterior limb of internal capsule, and parasagittal occipital cortex. Acute ischemic lesions were also found in the splenium of corpus callosum and right centrum semiovale. Magnetic resonance angiography (MRA) revealed absence of flow in the left internal carotid artery from skull base to the circle of Willis (Fig. 1a). The acute stroke was confirmed within 6 hours after symptom onset, the neurological deficit persisted, and no contraindication for thrombolysis was identified at that time, so the patient met the inclusion criteria for intra-arterial tissue plasminogen activator (tPA) treatment as stated in our institutional protocol for acute stroke. Conventional cerebral angiography was performed urgently, confirming the left internal carotid artery occlusion, which extended to the left middle cerebral artery (Fig. 1b). Intra-arterial tPA was then given selectively in repeated small boluses of 0.5mg for a total of 9mg (0.16mg/kg). The procedure was terminated 8 hours after onset of symptoms according to protocol. Partial recanalization of the left internal carotid artery and left middle cerebral artery was achieved (Fig. 1c). The patient tolerated the procedure without complications.

Investigations were then initiated to establish the etiology of the patient's stroke, including an echocardiogram and thrombophilia work-up. Transthoracic echocardiography revealed a large (12×8mm) oscillating mass on the left atrial side of the anterior mitral valve leaflet, mild mitral regurgitation, and small patent foramen ovale. *Streptococcus pneumoniae* was subsequently grown from three blood culture sets taken over a 21-hour period. Thus, the patient fulfilled clinical Duke criteria for definite IE.⁵ Unfraction-

ated heparin was therefore not initiated in this patient. Complete thrombophilia work-up was normal, except for a transiently elevated factor VIII.

Computed tomography of the head 12 hours after thrombolysis did not reveal intracranial hemorrhage. The patient's NIHSS score was 15 at this time. Repeat echocardiograms 2 days apart showed non-involvement of the aortic valve or root but persistence of the mitral valve vegetation. Follow-up cranial MRI and MRA 3 days after her neurological deterioration showed new diffusion-restricted lesions in the left cerebellum, thalamus, and frontal subcortical region, as well as evolution of the previously noted infarctions. There was no intracranial hemorrhage. MRA revealed complete recanalization of the previously occluded vessels (Fig. 1d). At that time (72h after tPA), her NIHSS score was 7.

Recurrent stroke and the size of the vegetations were considered indications for surgical management. The patient underwent debridement of three mitral valve vegetations, patch repair of the mitral valve, and closure of the patent foramen ovale. Transesophageal echocardiography intra-operatively revealed no obvious residual vegetation or leaflet perforation. The patient tolerated the procedure well without complications. Pathological analysis of the mitral valve vegetations revealed mostly fibrin thrombus with acute inflammation and some necrosis (Fig. 2). Special stains for microorganisms were negative. There was no microbial growth on culture of the vegetations. Post-operative echocardiograms failed to show residual vegetations. Computed tomography of the head 29h after cardiac surgery did not demonstrate new ischemic lesions, and there was no hemorrhage or hemorrhagic transformation of existing bland infarcts. Repeat blood cultures were negative. The patient gradually recovered neurologically with early rehabilitation and was discharged to an inpatient rehabilitation center with plans to complete intravenous antibiotic treatment for 6 more weeks. On discharge, she was ambulatory and conversant, with a NIHSS score of 5.

At 3-month follow-up, the patient's neurological examination revealed mild word-finding difficulties and some difficulties with attention and concentration. She had residual upper motor neuron right facial weakness, while the remainder of the cranial nerves were normal on examination. She had increased tone, mild weakness (4/5), and brisk reflexes in right upper and lower extremities. There were no abnormal cerebellar signs and sensory examination was intact. She had mild circumducted gait on the right.

DISCUSSION

Medical conditions with the potential complication of intracranial hemorrhage, such as IE, have been traditionally considered as a contraindication to thrombolytic ther-

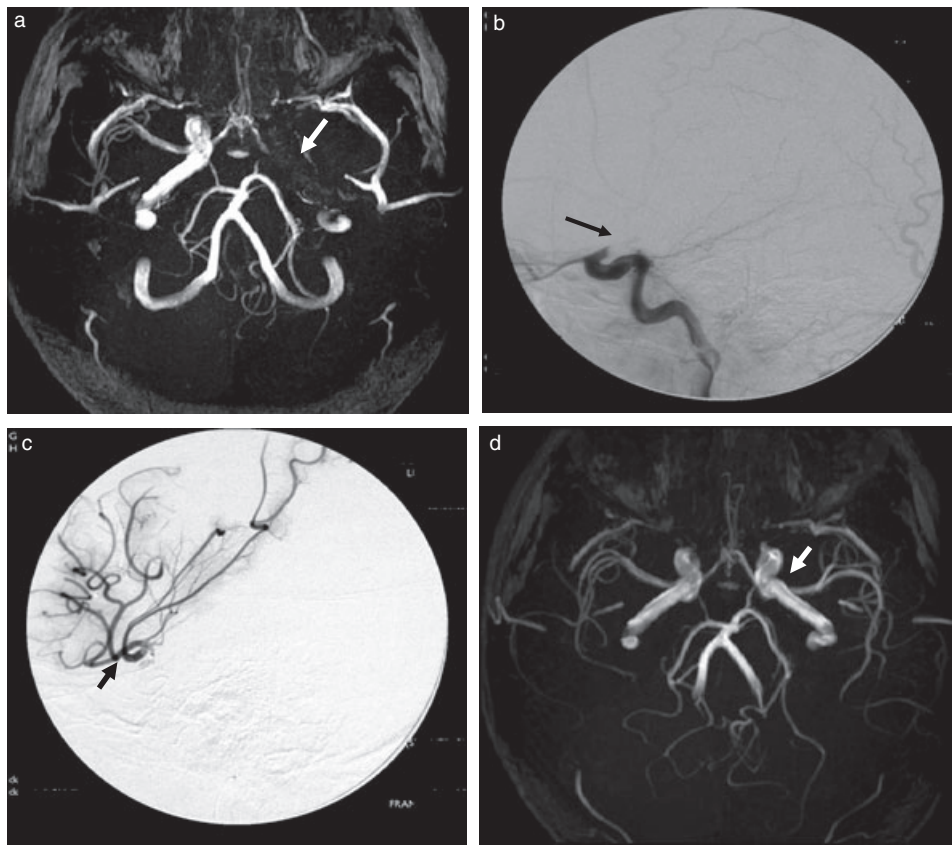


Figure 1: The patient's angiograms before and after thrombolysis. (a) Time-of-flight magnetic resonance angiogram (MRA) before thrombolysis showing a 13mm flow gap in the left internal carotid artery (LICA) bifurcation. (b) Lateral view of pre-thrombolysis contrast conventional cerebral angiogram (LICA injection) confirming the occlusion of LICA above the posterior communicating artery extending to the left middle cerebral artery (LMCA). (c) Lateral view of post-thrombolysis contrast conventional angiogram (LMCA injection) showing partial recanalization of the LMCA. (d) Time-of-flight MRA 3 days after thrombolysis showing complete recanalization of the occluded vessels.

apy for ischemic stroke. A recent case report described a successful administration of intravenous thrombolysis in a 56-year-old male who was subsequently diagnosed with infective mitral endocarditis.⁶ Although intracranial hemorrhage has been reported as a complication of IE in adults, the incidence is low at 2.7 to 7%.⁷

The most common mechanism of intracranial hemorrhage in IE is hemorrhagic transformation of bland infarcts. Predictors of hemorrhagic transformation include large infarct size and early use of anticoagulants after stroke presentation.⁸ Heparin therapy was not initiated after thrombolytic therapy in our patient because we reasoned that bacteria lodged in capillaries of the brain could cause vascular leaks that would transform into hemorrhage in the presence of heparin. Anticoagulation is not recommended in native valve IE.^{5,9} In our patient, the localized treatment with tPA resulted in a localized conversion of plasminogen to plasmin to effectively degrade the bacteria-fibrin clot. The rapid inhibition of plasmin by α_2 -anti-

plasmin in blood (half-life of plasmin <1min) decreases the bleeding risk to a relatively short time. The other mechanism of hemorrhage is rupture of mycotic aneurysms, which are found in only 0.3 to 1.8% of adults with IE. Rupture occurs in 1 to 2% of all IE patients.⁸ In a series of 57 pediatric patients with IE, there was only one reported case of cerebral hemorrhage secondary to a ruptured mycotic aneurysm.¹⁰

Intravenous tPA has been used to treat childhood IE, because it is believed to facilitate antibiotic penetration by degrading IE vegetations, which consist of fibrin, platelets, and the invading organism.¹¹ The low incidence of intracranial hemorrhage and the fact that the fibrin thrombus constitutes most of the vegetation according to pathological studies¹² raise the question whether IE should be a relative rather than an absolute contraindication in carefully selected pediatric patients who may potentially benefit from thrombolytic therapy (that is, in the absence of mycotic aneurysm and small infarct size).

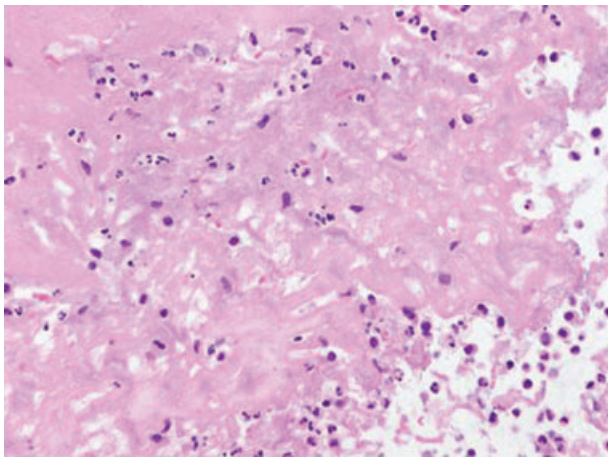


Figure 2: Histopathology of the patient's mitral valve vegetation. Hematoxylin and eosin stain of the thrombus showing polymorphonuclear leukocytes intermixed with fibrin-platelet thrombus (magnification $\times 200$).

IE-related neurological complications occur in 20 to 40% of adult patients^{13,14} and have been shown to be associated with poor outcome, with a mortality rate as high as 58%.¹⁴ Published data on neurological complications related to childhood IE are scarce. In a recent review of 115 children with IE, seven (6%) had a stroke.¹⁵ Unlike our patient, they all presented with stroke after the diagnosis of IE and after cardiac surgery. Neurological outcome at 4 to 6 months after the stroke was reported in five of the seven patients. Poor neurological outcome was associated with very young age, absence of congenital heart disease, and mitral valve involvement.¹⁵ Two of the five patients had no deficit and did not have any of the risk factors. Our patient was a young adolescent but had the other two risk factors for poor outcome. Nevertheless, she had a remarkable neurological recovery at 3 months after her stroke.

CONCLUSION

We believe that localized thrombolytic therapy contributed to a favorable outcome in our patient with IE, complete occlusion of the left internal carotid artery, and multiple intracerebral infarcts. This case suggests that fibrinolysis may be safe in selected cases and may have a therapeutic role in childhood IE-related acute ischemic stroke.

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