Endovascular thrombolysis for pediatric cerebral sinus venous thrombosis with tissue plasminogen activator and abciximab

Case report

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Cerebral sinus venous thrombosis (CSVT) is a relatively rare but potentially devastating disease. Medical management of CSVT with systemic anticoagulation has been the mainstay treatment strategy with these patients. However, some patients may not respond to this treatment or may present with very severe symptoms indicating more aggressive management strategies. The authors present the case of a pediatric patient who presented with severe CSVT, who underwent successful recanalization with endovascular tissue plasminogen activator (tPA) and abciximab. To the authors’ knowledge there are no cases of endovascular thrombolysis for CSVT described in the literature in which abciximab has been used in conjunction with tPA. The authors also review the literature regarding the agents used and outcome in pediatric patients with CSVT after endovascular thrombolysis. The use of abciximab in conjunction with tPA may be considered in patients whose blood is hypercoagulable and in whom the treatment strategy is to obtain acute recanalization and long-term venous patency. However, the use of adjunctive agents increases the risk of hemorrhagic complications and must be done judiciously.

Key Words • cerebral sinus venous thrombosis • abciximab • superior sagittal sinus thrombosis • tissue plasminogen activator • endovascular thrombolysis • vascular disorders

Abbreviations used in this paper: CSVT = cerebral sinus venous thrombosis; ICH = intracerebral hemorrhage; SSS = superior sagittal sinus; SVG = saphenous vein graft; tPA = tissue plasminogen activator.

Intracranial pressure due to normalization of cerebral blood drainage.

Various authors have shown successful management of CSVT with endovascular treatment accompanied by the administration of urokinase or tissue plasminogen activator (tPA).15 Abciximab (a glycoprotein IIb/IIIa receptor antagonist) has shown promise in the treatment of experimental CSVT in rats, but to our knowledge there are no reported cases in which adjuvant tPA and abciximab have been used for the treatment of severe CSVT.15 We describe the case of a pediatric patient who presented with widespread thrombosis including CSVT, who underwent successful recanalization with endovascular tPA and abciximab administration.

Case Report

History and Examination. This 16-year-old boy presented to the emergency room with a 3-week history of worsening headaches. He had a history of Stage III Hodgkin lymphoma with no B symptoms (he had completed therapy 6 years earlier). The headaches were right frontal
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in location and were worst in the mornings. There was also some associated phonophobia, occasional nausea and vomiting, but no photophobia. For the last 3 days he had also noticed decreased sensation in the left arm and leg.

On examination the patient was alert and oriented. Motor examination revealed left-sided weakness in the upper and lower extremities (4/5). There was a marked decrease of light touch sensation in the left arm and leg as well.

Neuroimaging Investigation. Brain MRI and MR venogram depicted multiple areas of signal loss within the superior sagittal sinus (SSS), and right transverse and sigmoid sinus thrombosis (Fig. 1). The MRI study showed a small right parietal venous ischemic infarct but no hemorrhage. Further investigation also uncovered right popliteal and posterior tibial thrombosis and a thrombus in the right atrium. The patient was started on a heparin drip. Three days later, in spite of optimized heparin dosage, the left-sided weakness had worsened and an MRI study depicted a slight interval increase in the size of the parietal venous infarct.

Based on the extent of sinus venous thrombosis and unresponsiveness to medical management, it was decided to treat this patient with transvenous thrombolysis of the SSS and right transverse sigmoid thrombosis.

Endovascular Management. A nick incision was made over the region on the right femoral artery, accessed with a single-wall needle technique. A Bentson wire was passed into the femoral vein and a 7-Fr sheath was placed in the vein connected to a continuous heparinized flush solution. The guide catheter was transnavigated through the transvenous route to the jugular bulb at the base of the skull on the right. A microcatheter was then transnavigated coaxially through the guide catheter over a 0.14 microwire to select the middle third of the SSS. The tPA and abciximab was then administered in 2-mg aliquots (total dosages: tPA 8 mg and abciximab 12 mg) and progressive revascularization of the SSS and right sigmoid sinus was effected. Control venous angiography confirmed complete revascularization of the sinuses (Fig. 2).

Posttreatment Course. The patient had gradual improvement in the left-sided weakness and paresthesias following the intervention, and there were no hemorrhagic complications. He was discharged to a rehabilitation center 8 days later, and a CT venogram obtained 4 months posttreatment showed patent sinuses and no venous infarcts (Fig. 2). The patient has received 12 months of follow-up, with improving neurological status and no cognitive deficits.

Discussion

Although it is a relatively rare condition, CSVT is potentially devastating. The Canadian Pediatric Ischemic Stroke Registry reported an annual incidence of 0.34 cases of CSVT per 100,000 children, rising to 0.67 per 100,000 persons when neonates were included. This study reported death in 8% and neurological deficits in 41%. Malignancies are a risk factor for CSVT, and this condition is a known complication in the treatment for leukemia or non-Hodgkin lymphoma. Investigators at the Mayo Clinic recently reported an experience of 9 cases of CSVT in a retrospective sample of 200 patients with acute lymphoblastic leukemia or non-Hodgkin lymphoma. All patients had previously been treated with t-PA asparaginase. Each patient’s CSVT was treated with low-molecular-weight heparin. Of the 4 patients who were available for long-term follow-up, all had normal or near-normal neuropsychological outcomes.

Systemic anticoagulation has been the mainstay in the treatment of CSVT; however, cases in which medical management has been unsuccessful or emergency intervention is required have driven the development of direct thrombolytic therapy via microcatheter. Although there have been no randomized controlled trials as of this writing, patients receiving direct thrombolysis with urokinase or tPA have generally experienced excellent recovery. Mechanical thrombectomy is another option that is currently undergoing clinical investigation. There are only a few cases of direct thrombolysis for CSVT in children, and these are mostly documented in case reports or small case series. Most practitioners have used urokinase, which has been replaced by tPA in recent years (Table 1). These patients generally have favorable outcomes, with excellent recovery and no associated iatrogenic intracerebral hemorrhage (ICH). However, the long-term outcomes in these patients have only rarely been reported in the literature.

We could find no previous reports in the cerebrovascular literature of adjudant local abciximab being used with tPA for the management of CSVT. Röttger and colleagues studied the effect of intravenous abciximab in experimentally induced SSS thrombosis in rats, and found that compared with tPA and enoxaparin, abciximab had the best clinical outcome and the most prolonged progressive recanalization beyond the 1st postoperative day.

A recent nonrandomized prospective study of intravenous abciximab used in conjunction with intraarterial tPA in 20 patients with vertebralbasilar occlusion found that it yielded a high recanalization rate (85%). Another study of 47 prospective patients found that those who received this combination, with the addition of percutaneous transluminal angioplasty and/or stent insertion for severe residual stenosis, had improved neurological outcomes over a retrospective cohort treated by tPA alone (34% vs 17%).

Fig. 1. Left: A reconstructed MR venogram depicting a noncontinuous SSS (arrows). Right: Sagittal T1-weighted MR image showing an isointense clot in the SSS (arrow).
The management of CSVT with endovascular thrombolysis carries the risk of hemorrhagic complications, especially if a combination of drugs is used. Qureshi et al. reported on 7 patients who developed ICHs associated with neurointerventional procedures in which a combination of antithrombotic agents including abciximab were used. It is important to note, however, that the patients reported in that series had angio-occlusive disease leading to a high risk of reperfusion injury with intervention. The use of multiple antithrombotic drugs in this setting may greatly increase the risk of ICH.

Abciximab has shown promise when used to treat thrombo-occlusive saphenous vein graft (SVG) disease after cardiac bypass surgery. Pretreatment with abciximab has been shown to decrease the thrombus burden in the SVG before percutaneous intervention is attempted. Routine use of abciximab for elective percutaneous coronary intervention to reopen thrombosed SVGs has also been shown to improve the long-term outcome in patients with diabetes (who have historically had worse outcomes than nondiabetic patients). Kirby and colleagues also noted the long-term efficacy of abciximab in preventing reocclusion of venous thrombosis. They reported a small case series of critically ill pediatric patients who underwent mechanical thrombectomy with abciximab administration for central venous thrombosis. Their intervention led to a near-normal venous flow pattern and subsequent long-term normal central veins in most of their patients. Our patient had a history of Hodgkin lymphoma and had developed venous thrombosis in various parts of his body, with no known precipitating factors. In patients with this hypercoagulable state, we believe that supplementing tPA

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases</th>
<th>Age, Sex</th>
<th>Agent</th>
<th>Dose</th>
<th>Outcome</th>
<th>FU</th>
</tr>
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<tbody>
<tr>
<td>Higashida et al., 1989</td>
<td>1</td>
<td>10 yrs, M</td>
<td>urokinase</td>
<td>1000 U/hr × 2 hrs</td>
<td>normal development at 3 yrs</td>
<td>6 wks</td>
</tr>
<tr>
<td>Griesemer et al., 1994</td>
<td>1</td>
<td>9 yrs, M</td>
<td>urokinase</td>
<td>470,000 U/75 mins</td>
<td>normal, except weakness of rt triceps &amp; rt ankle dorsiflexion</td>
<td>2 yrs</td>
</tr>
<tr>
<td>Gebara et al., 1995</td>
<td>1</td>
<td>3 yrs, F</td>
<td>rtPA</td>
<td>25,000 U/10 mins × 7</td>
<td>normal</td>
<td>9 mos</td>
</tr>
<tr>
<td>Del-Rio Camacho et al., 2001</td>
<td>1</td>
<td>10 days, M</td>
<td>tPA</td>
<td>0.2-mg/kg bolus, 0.5 mg/kg/hr × 3 hrs</td>
<td>excellent</td>
<td>2 wks</td>
</tr>
<tr>
<td>Gebara &amp; Everett, 2001</td>
<td>1</td>
<td>4 yrs, M</td>
<td>urokinase</td>
<td>125,000 U/80 mins</td>
<td>excellent</td>
<td>2 wks</td>
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<td>Zerah et al., 2001</td>
<td>1</td>
<td>12 yrs, F</td>
<td>urokinase</td>
<td>50,000 U bolus, 5000 U/hr</td>
<td>normal</td>
<td>1 day</td>
</tr>
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<td>Wasay et al., 2006</td>
<td>3</td>
<td>3.5 yrs, M</td>
<td>urokinase + tPA</td>
<td>30,000 U urokinase, 0.5 mg/kg/hr tPA</td>
<td>death 6 hrs after tPA infusion w/o hemorrhage</td>
<td>NA</td>
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<tr>
<td>Philips et al., 1999</td>
<td>1</td>
<td>14 yrs, F</td>
<td>urokinase</td>
<td>200,000 U</td>
<td>excellent</td>
<td>NA</td>
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<tr>
<td>Wasay et al., 2001</td>
<td>1</td>
<td>4 yrs, M</td>
<td>urokinase</td>
<td>50,000-U bolus, 10,000 U/hr</td>
<td>normal on discharge</td>
<td>NA</td>
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<tr>
<td>Horowitz et al., 1995</td>
<td>2</td>
<td>6 yrs, F</td>
<td>urokinase</td>
<td>50,000-U bolus, 100,000 U/hr × 84 hrs</td>
<td>excellent</td>
<td>NA</td>
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<tr>
<td></td>
<td></td>
<td>12 yrs, F</td>
<td>urokinase</td>
<td>500,000-U bolus, 60,000 U/hr × 72 hrs</td>
<td>excellent</td>
<td>NA</td>
</tr>
</tbody>
</table>

* FU = follow-up; NA = not applicable; rtPA = recombinant tPA.
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with abciximab for endovascular thrombolysis increases the chances of obtaining long-term recanalization.

Endovascular thrombolysis is a safe and effective treatment modality in pediatric patients with severe symptomatic CSVT. The use of abciximab in conjunction with tPA may be considered in patients whose blood is hypercoagulable, and in whom the treatment strategy is to obtain acute recanalization and long-term venous patency. However, the use of adjunctive agents increases the risk of hemorrhagic complications and must be done judiciously.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Singer, Khan, Ladner, Jordan. Acquisition of data: Khan, Ladner, Satti, Ehtesham, Jordan. Drafting the article: Khan, Ladner, Satti, Ehtesham. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Singer. Study supervision: Singer.

References


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