Endovascular thrombolysis for symptomatic cerebral venous thrombosis

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Object. The authors sought to treat potentially catastrophic intracranial dural and deep cerebral venous thrombosis by using a multimodality endovascular approach.

Methods. Six patients aged 14 to 75 years presented with progressive symptoms of thrombotic intracranial venous occlusion. Five presented with neurological deficits, and one patient had a progressive and intractable headache. All six had known risk factors for venous thrombosis: inflammatory bowel disease (two patients), nephrotic syndrome (one), cancer (one), use of oral contraceptive pills (one), and puerperium (one). Four had combined dural and deep venous thrombosis, whereas clot formation was limited to the dural venous sinuses in two patients. All patients underwent diagnostic cerebral arteriograms followed by transvenous catheterization and selective sinus and deep venous microcatheterization. Urokinase was delivered at the proximal aspect of the thrombus in dosages of 200,000 to 1,000,000 IU. In two patients with thrombus refractory to pharmacological thrombolytic treatment, mechanical wire microsnare maceration of the thrombus resulted in sinus patency. Radiological studies obtained 24 hours after thrombolysis reconfirmed sinus/vein patency in all patients. All patients' symptoms and neurological deficits improved, and no procedural complications ensued. Follow-up periods ranged from 12 to 35 months, and all six patients remain free of any symptomatic venous reocclusion. Factors including patients' age, preexisting medical conditions, and duration of symptoms had no statistical bearing on the outcome.

Conclusions. Patients with both dural and deep cerebral venous thrombosis often have a variable clinical course and an unpredictable neurological outcome. With recent improvements in interventional techniques, endovascular therapy is warranted in symptomatic patients early in the disease course, prior to morbid and potentially fatal neurological deterioration.

Key Words • cerebral vein • thrombosis • endovascular surgery • urokinase • clot fragmentation

Cerebral venous thrombosis results from thrombosis of cortical and deep veins and/or intracranial venous sinuses. The spectrum of signs and symptoms connected with cerebral venous thrombosis may be broad; it is associated with a variety of conditions, including infection, coagulation disorders, chronic inflammatory disease, and trauma. If the disease is unrecognized, a delay in treatment may result in cerebral edema, intracranial hypertension, cerebral ischemia, and hemorrhagic infarction, resulting in rapid neurological deterioration, coma, and even death. 

The development and availability of more sophisticated diagnostic tools, such as computerized tomography (CT) scanning, magnetic resonance (MR) imaging, and MR venography, have facilitated the prompt diagnosis and treatment of cerebral venous thrombosis and have resulted in improved patient outcome. 

Despite earlier detection, the clinical course of this disease may still be unpredictable with medical management. 

Reported rates of total recovery have ranged from 52 to 85.7%, whereas mortality rates among some patient populations have ranged from 9 to 33%. 

Medical and surgical therapeutic strategies directed at intracranial venous thrombosis have included systemic anticoagulation therapy, 

Cerebrospinal fluid drainage, and surgical sinus thrombectomy and have yielded variable levels of success. 

Interventional neuroradiological techniques provide rapid access to the cerebral venous system and offer the ability to treat the thrombus directly while limiting iatrogenic complications. 

Furthermore, the development of more advanced microcatheters for superselective catheterization has provided interventionalists with better access to the deep cerebral venous system, in which thrombosis is usually associated with a dismal prognosis. 

Failure of thrombolytic therapy in selected cases has been attributed to the age and constitution of the clot.

Mechanical clot maceration in conjunction with administration of fibrinolytic agents has succeeded in restoring
TABLE 1
Clinical presentation of patients with symptomatic cerebral venous thrombosis*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Risk Factors for CVT</th>
<th>Presenting Neurological Status</th>
<th>Presenting GCS Score</th>
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<tr>
<td>1</td>
<td>35, F</td>
<td>IBD</td>
<td>intractable headache</td>
<td>headache, diplopia, visual field changes</td>
<td>15</td>
</tr>
<tr>
<td>2††</td>
<td>19, F</td>
<td>OCP</td>
<td>headache, diplopia, visual field changes</td>
<td>hemiparesis, coma</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>14, F</td>
<td>IBD</td>
<td>hemiparesis, coma</td>
<td>hemiparesis, somnolent</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>26, F</td>
<td>postpartum</td>
<td>hemiparesis, somnolent</td>
<td>bilat CN VI palsies, seizures</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>29, M</td>
<td>nephrotic syndrome</td>
<td>bilat CN VI palsies, seizures</td>
<td>hemiparesis, coma</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>75, M</td>
<td>cancer (melanoma)</td>
<td>hemiparesis, coma</td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

* CN = cranial nerve; CVT = cerebral venous thrombosis; IBD = inflammatory bowel disease; OCP = oral contraceptive pills.
† This case has been reported previously.2

Clinical Material and Methods

Six patients (two male and four female) aged 14 to 75 years (mean 33 years) presented with progressive symptoms from cerebral venous thrombosis (Table 1). All had risk factors for venous thrombosis, including inflammatory bowel disease (two patients), nephrotic syndrome (one), cancer (one), childbirth (one), and oral contraceptive use (one). Five presented with progressive neurological deficits, including visual acuity changes (one patient), hemiparesis (three), and altered mental status (two), and one patient had a progressive and intractable headache. Three patients presented with a Glasgow Coma Scale (GCS) score of 15, whereas the remaining three presented with scores of 7, 14, and 5, respectively (median 10). After confirmation of intracranial venous thrombosis on CT scanning, MR imaging, and MR venography, all patients were started on intravenously administered heparin as part of their preendovascular procedure therapy.

Patients underwent diagnostic cerebral arteriography followed by transvenous catheterization and selective sinus and deep venous microcatheterization. All patients underwent right femoral vein and ipsilateral femoral artery catheterization (in which single-walled and double-walled puncture techniques, respectively, were used) followed by heparin therapy after access was established. A late venous phase cerebral arteriogram was obtained. On the venous side, a microcatheter (Tracker-18; Target Therapeutics, Fremont, CA) was advanced through a catheter (No. 7 French Berenstein; Bard, Billerica, MA) and placed at the level of the right sigmoid sinus.

Once the extent of cerebral venous thrombosis was established, the microcatheter was advanced, and selectively maneuvered into the appropriate dural venous sinuses and/or deep venous structures, paying special attention to manipulation of the devices in venous structures more predisposed to catheter penetration. No catheters other than those mentioned previously and those in standard use for arterial catheterization were utilized for superselective catheterization of the venous structures. Advancement of the microcatheter through the clot was followed by the delivery of approximately 50,000 IU of urokinase every 15 minutes at the cephalad aspect of the thrombus by using the pulse-spray technique. If there was no change in the venographic appearance of the thrombus after delivery of approximately 200,000 IU of urokinase, mechanical disruption of the thrombus was performed by dragging a microsnare (Amplatz Goose Neck microsnare; Microvena, White Bear Lake, MN, Fig. 1) repeatedly over the thrombus surface. After clot maceration, urokinase infusion was reinitiated and continued until venous patency or a total dosage of 1,000,000 IU of urokinase was reached. Angiographic studies performed at the conclusion of the thrombolytic procedure allowed us to de-termind sinus/venous patency and the arteriovenous relationship, especially with regard to transit time. The femoral sheaths were maintained for 24 hours after the procedure, and the patients continued to receive systemic anticoagulation therapy with intravenously administered heparin.

Four patients suffered combined dural and deep thrombosis, whereas clot formation was limited to the dural venous sinuses in two patients. In the four patients with deep cerebral thrombosis, clots were noted in the internal cerebral veins (three vessels), straight sinus (three), vein of Galen (one), and inferior sagittal sinus (one). Of the six patients treated, all underwent transvenous catheterization and received urokinase infusions of 200,000 to 1,000,000 IU. Three patients underwent superselective catheterization of their straight sinus, and two were treated with mechanical snare maceration of their urokinase-resistant thrombus. One of these underwent both superselective deep venous catheterization and mechanical clot maceration (Case 1, Table 2). Some restoration of sinus/deep venous patency was achieved in all patients as confirmed on postprocedural angiographic studies and on MR imaging and MR venography prior to hospital discharge. At dis-
Charge all of the patients had improved neurologically. Five patients were independent with respect to cognitive and motor function, and two, one of whom required assistance with activities of daily living, had residual hemiparesis. Complications that occurred during the hospital stays included aspiration pneumonia (one), cystitis (two), and complicated cystitis with hematuria (one).

**Illustrative Cases**

**Case 5**

This 29-year-old man with a known history of nephrotic syndrome and a positive anticardiolipin antibody screen presented after several months of headaches. Just prior to admission, his persistent left frontal headaches changed to a frontoorbital location. This was followed by acute onset of nausea, vomiting, visual changes, dizziness, and gait instability. After treatment with sumatriptan succinate he became increasingly lethargic and somnolent. On neurological examination he was noted to have a left-sided homonymous hemianopsia and marked left-sided extinction. A head CT scan revealed a right temporal lobe hemorrhagic infarction and a sinus thrombosis that were confirmed on MR imaging (Fig. 2). Despite medical management, including steroid administration, heparin anticoagulation therapy, and volume expansion, his neurological status continued to deteriorate. On Day 3 of his hospitalization he underwent angiographic evaluation. Cerebral arteriography demonstrated thrombosis of the left internal jugular vein, left sigmoid sinus, and bilateral transverse sinuses. Transvenous microcatheterization of the left internal jugular vein was performed, followed by infusion of 200,000 IU of urokinase directly into the thrombus. Systematic advancement of the microcatheter with concomitant urokinase infusion resulted in progressive lysis of the intraluminal clot and reopening of the sinuses.

Results of the patient’s neurological examination improved immediately after the endovascular therapy, although bilateral abducens nerve palsies persisted. He continued to receive intravenous heparin anticoagulation therapy, which was converted to a course of oral warfarin prior to discharge from the hospital. Twelve months after discharge he remains neurologically intact except for bilateral partial sixth cranial nerve palsies.

**Case 4**

Ten days postpartum this 26-year-old woman developed medically refractory bifrontal headaches. At 20 days after delivery she investigated by a combination of medical and surgical management, including steroid administration, heparin anticoagulation therapy, and volume expansion, his neurological status continued to deteriorate. On Day 3 of his hospitalization he underwent angiographic evaluation. Cerebral arteriography demonstrated thrombosis of the left internal jugular vein, left sigmoid sinus, and bilateral transverse sinuses. Transvenous microcatheterization of the left internal jugular vein was performed, followed by infusion of 200,000 IU of urokinase directly into the thrombus. Systematic advancement of the microcatheter with concomitant urokinase infusion resulted in progressive lysis of the intraluminal clot and reopening of the sinuses.

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postpartum she developed an acute left-sided hemiparesis and dysarthria. Her head CT scan revealed a hypodensity involving the right basal ganglia and thalamus consistent with infarction. This was confirmed on MR imaging and MR venography, which revealed a left transverse sinus, straight sinus, and bilateral internal cerebral vein thrombosis (Fig. 3). Because of these findings and her rapidly deteriorating neurological condition, the patient underwent emergency diagnostic arteriography followed by transvenous catheterization. Urokinase was initially infused into the left transverse sinus. After partial patency was achieved, superselective catheterization of the proximal straight sinus was performed with additional infusion of urokinase (Fig. 4). After a total infusion of 1,000,000 IU of urokinase over 4 hours, patency of the deep venous system and transverse sinuses was achieved. Her mental status improved immediately postprocedure. She continued to receive systemic anticoagulation therapy, which was subsequently converted to oral warfarin. By the time of discharge, she displayed markedly improved strength in her left side, was ambulatory with assistance, and had normal speech. Five months after discharge her MR venographic study demonstrated open sinuses (Fig. 3), and she was living independently.

Case 1

This 35-year-old woman with a known history of ulcerative colitis presented with a 4-day history of bifrontal headache followed by the acute onset of right-sided hemiparesis with hypesthesia, vomiting, and diplopia. Brain MR imaging revealed thrombosis of her superior sagittal sinus (SSS). She was treated with intravenously administered heparin anticoagulation therapy along with hydration and steroid medication, and her neurological examination results returned to normal. Her anticoagulation therapy was converted to oral warfarin and she was discharged home.

Four weeks after discharge, her oral warfarin therapy was temporarily discontinued for performance of a colonoscopy procedure. Two days later she returned to the hospital with headache, nausea, and vomiting. Magnetic resonance imaging analysis revealed a thrombosed poste-
Cerebral venous thrombosis is uncommon and has an unpredictable clinical course. In this report we describe six patients who improved after multimodality endovascular therapy of their cerebral venous thrombosis. Because intraparenchymal changes can be seen on presentation with venous occlusion on MR imaging, rapid diagnosis is essential and immediate treatment is imperative in patients with progressive neurological deterioration. Although earlier reports have indicated improved outcomes, it was not until 1991 that a prospective randomized clinical trial showed 80% complete recovery with no deaths in the group receiving anticoagulation therapy compared with a 10% complete recovery and 30% dead in the group receiving placebo. Subsequent reports have not shown that the use of systemic anticoagulation therapy consistently leads to successful outcomes. Investigators have attributed this unpredictability to a variety of factors including the cause of procoagulant activity (Behçet’s disease, puerperium), rate of thrombus development, and involvement of the deep venous system.

Because of the high variability and unpredictability of systemic anticoagulation therapy and the relative risks of operative thrombectomy, clinicians have explored a minimally invasive thrombolytic approach in which local and systemic fibrinolysis are used. To avoid perfusing ischemic or infarcted brain with fibrinolytic agents via systemic administration, methods of direct infusion of thrombolytic agents into the thrombosed vessel were considered. Higashida, et al., and Scott, et al., infused urokinase directly into the SSS via the anterior fontanel and a midline frontal craniectomy, respectively. Although Scott, et al., considered intervention via femoral vein catheterization, they had less confidence in this angiographic technique available at that time. Subsequently, Barnwell and colleagues selectively lysed dural sinus thrombi with urokinase via a transjugular route in three patients with progressive neurological deterioration.

With the improvement in microcatheter systems and interventional techniques, rapid access to the dural sinuses via a transfemoral route has become the established method for administering anticoagulation therapy. The selective delivery of fibrinolytic agents to the thrombosed dural sinus, resulting in radiographically confirmed patency of the vessel, appears to correlate with a more rapid and predictable improvement in symptoms. In the larger series of patients who were endovascularly treated, Smith and colleagues demonstrated sinus patency in all cases and attenuation or improvement of neurological deficits in six of seven patients treated. Horowitz, et al., showed sinus patency in 11 of 12 patients, and good to excellent clinical outcome in 10 (91%) of 11.

Recent advances in imaging techniques have allowed earlier diagnosis of cerebral venous thrombosis and have helped identify a subset of patients with a predictably worse outcome, namely those with associated deep venous thrombosis. Much of the earlier work on intracranial venous thrombosis centered around dural sinus thrombosis, but more recent observations indicate that thrombus extending beyond the superficial sinuses (deep cerebral veins or cortical veins) is an independent predictor of poor outcome. Several investigators have demonstrated that occlusion of only the SSS does not cause a reduction in the regional parenchymal blood flow, but that occlusion of the ascending veins must exist for adverse effects on regional parenchymal blood flow to occur. The attenuation of the rapid neurological deterioration in the patient in Case 4 after treatment with superselective catheterization of her straight sinus and thrombolysis coincides with previous observations. Although this patient may have recovered with systemic heparinization alone, the temporal relationship between her rapid neurological deterioration and subsequent improvement after thrombolysis suggests that direct thrombolytic therapy to her deep cerebral venous system facilitated her excellent outcome.

The intermittent failure of fibrinolytic agents to dissolve venous thrombus adequately and the usefulness of concomitant mechanical thrombus disruption has been recognized in a variety of extracranial clinical circumstances. Combined mechanical and pharmacological (pharmacomechanical) thrombolysis of thrombosed dialysis grafts has demonstrated a high degree of success with limited iatrogenic complications. Furthermore, mechanical thrombolysis in combination with fibrinolytic agent administration has resulted in rapid improvements in hemodynamics and blood oxygenation in patients with massive pulmonary embolisms.

Other investigators have recognized that intracerebral mechanical clot fragmentation with the microinfusion catheter has increased surface area of the intracerebral thrombus and made it more amenable to pharmacological treatment. Successful mechanical disruption of intracranial venous thrombus by using the microcatheter and its guidewire has been reported. However, in our series the microsnare showed significant advantages over the guidewire and microcatheter in macerating the thrombus. Unlike the guidewire and microcatheter, the increased surface area resulting from the snare’s loop con-
figuration and its ability to be repeatedly opened and closed allows for rapid and efficient clot fragmentation, whereas its flexibility and ease movability do not decrease its potential for vessel injury as compared with the microcatheter alone.\textsuperscript{2,4} Finally, the age of the thrombus has been implicated in its response to pharmacological thrombolysis.\textsuperscript{3,24} In the patient in Case 1, this may have been a significant factor because thrombolysis was performed 4 weeks after the initial symptoms. Mechanical clot maceration may help reduce endogenous complications by increasing the thrombus surface area exposed to pharmacological treatment, thus resulting in lower doses of fibrinolytic agents and a shorter procedure time.\textsuperscript{2}

In a review of all reported cases of endovascular treatment of cerebral venous thrombosis in the English literature, we found consistent clinical improvement and an overall improvement rate of 93\% after compilation of the cases into a single group (Table 3). Adding the patients from the present report to the group increases the improvement rate to 94\% with only a 2\% mortality rate. This rate of improvement appears to be uniformly more reproducible with endovascular thrombolysis than with systemic anticoagulation. One theoretical pitfall associated with endovascular thrombolytic therapy may arise in patients with concomitant intraparenchymal hemorrhages, in whom heparin treatment has been shown to be contraindicated.\textsuperscript{16} However, in several series, including ours, there have been no significant intracerebral hemorrhagic complications in this select group of patients after they were treated with endovascular thrombolytic agents.\textsuperscript{24,32,57} This is thought to be due to the relatively rapid metabolism of the thrombolytic agent and, thus, the relatively low arteriolar concentration of the fibrinolytic agent. Furthermore, as described previously, mechanical maceration of the thrombus reduces the total volume of thrombolytic agent required for adequate thrombolysis. Unlike heparin anticoagulation therapy, thrombolytic agents can promptly accomplish two therapeutic goals: 1) attenuation of thrombus progression; and 2) restoration of venous flow. Furthermore, because of the flexible catheters and the rapid systemic inactivation of urokinase, the systemic and intracranial complications appear to be no more than those of systemic anticoagulation in the acute period.

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Improved</th>
<th>Worse</th>
<th>Dead</th>
</tr>
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<tbody>
<tr>
<td>Barnwell, et al., 1991</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tsai, et al., 1992</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith, et al., 1994</td>
<td>6</td>
<td>1</td>
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<td>Horowitz, et al., 1995</td>
<td>11</td>
<td>1</td>
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<td>Gurley, et al., 1996</td>
<td>2</td>
<td></td>
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<td>Gersten, et al., 1997</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Kim &amp; Suh, 1997</td>
<td>9</td>
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<td>Rael, et al., 1997</td>
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<td></td>
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<tr>
<td>D’Alise, et al., 1998</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Keuther, et al., 1998</td>
<td>1</td>
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<tr>
<td>Niwa, et al., 1998</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>40 (93%)</td>
<td>2 (5%)</td>
<td>1 (2%)</td>
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</table>

Conclusions

Therapy for cerebral venous thrombosis remains controversial, and there is no clear consensus on an approach that optimizes patient outcome. There has been only one randomized prospective clinical study\textsuperscript{16} evaluating any treatment option for this disease, and further assessment of the potential role and benefit of aggressive and early endovascular therapy for cerebral venous thrombosis must be pursued. However, given the data presented in our study, endovascular thrombolysis for both dural sinus and deep cerebral veins appears to have the most obvious benefits in the setting of a rapid and progressive neurological deterioration. The results in this group of patients support the use of an interventional neuroradiological approach to promptly restore cerebral venous outflow. Advances in endovascular techniques capable of superselective fibrinolytic and mechanical thrombolysis, including microcatheter systems and mechanical snares, have extended the therapeutic boundaries for this previously unpredictable and potentially catastrophic disease.

Disclosure

The authors have no financial interest in the instruments or methodology presented in this manuscript.

References

Endovascular thrombolysis for venous thrombosis


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