Ischemic stroke is often caused either by embolization of intravascular debris to cerebral vessels or by hemodynamic and thrombotic consequences of intracranial vascular stenosis. The following review discusses medical management, endovascular treatment, and future research for each of these broad areas of ischemic stroke.

**TREATMENT OF ACUTE STROKE**

At the University at Buffalo Department of Neurosurgery, endovascular technique for the treatment of acute stroke has evolved with laboratory research, participation in clinical trials, and clinical experience (Table 20.1). From 1994 to 1996, the primary method of treatment was intra-arterial (IA) injection of urokinase or prourokinase. In 1997, IA injection of tissue plasminogen activator (tPA) and endovascular methods for mechanical clot lysis (angioplasty, clot perturbation with a microwire, and snare retrieval) were added to this regimen. Use of the current thrombolytic agent, reteplase (1–4 U), began in 1999. Since 2001, combination treatments have been used. The doses, timing, and sequences are based on patient-specific factors and intraprocedural imaging findings. The current regimen includes pharmaceuticals (low-dose heparin, reteplase, and IIb–IIIa inhibitors), plus mechanical clot retrieval with progressive generations of the Merci device (Concentric Medical, Mountain View, CA), and a stent for unsuccessful Merci clot retrieval.14,19

Patients are triaged for therapy on arrival at the emergency department. The elapsed time from onset and findings on computed tomographic perfusion imaging are used to guide treatment. Those patients presenting within 3 hours of symptom onset are treated with intravenous tPA if the National Institutes of Health Stroke Scale (NIHSS) score is at most 8, and with combination IA therapies if the NIHSS score is greater than 8. Patients treated from 3 to 6 hours receive IA thrombolytics or combination mechanical therapies. Beyond 6 hours, patients with ischemic lesions within the anterior circulation may still benefit from endovascular therapies, provided the region of absent perfusion (the “black hole” or core infarction) is not located primarily within the basal ganglia and is not greater than 33% of the region at risk.10 If the area of absent perfusion is greater than 33%, with progressively larger regions of absent perfusion, there is increasing risk for neurological worsening from intracranial hemorrhage. Therefore, as the size of the “black hole” increases, the combination of therapies is progressively more conservative.10 Other patient-specific factors, such as age and medical comorbidities as well as the type and severity of neurological deficit, are important for decision making. For patients with posterior fossa infarctions, endovascular therapies are considered until 12 to 24 hours have passed. In such cases, magnetic resonance imaging scans with diffusion-weighted, apparent-diffusion coefficient and magnetic resonance angiography sequences are used to guide patient selection.

Recently, stent placement has been used as an adjunctive treatment for recanalization of acute cerebrovascular occlusions after failure of other mechanical or pharmacological maneuvers. In our initial experience (in combination with three other medical centers), the overall rate of stent-assisted recanalization (thrombolysis in myocardial infarction [TIMI] 2 or 3 flow) was 79% (15 of 19 lesions).14 Among 19 lesions (18 patients), TIMI 2 or 3 flow was achieved in 100% of lesions limited to the middle cerebral artery (MCA) (9 patients) or within the vertebrobasilar system (3 patients). However, for lesions that included internal carotid artery (ICA) occlusion, TIMI 2 or 3 flow was achieved in only 3 of 7 patients. Concurrent with recanalization, 50% of patients with lesions limited to the MCA or vertebrobasilar system and 33% of patients with lesions including the ICA had clinical improvement of 4 or more NIHSS points within 24 hours after the procedure. In addition, four of six patients treated with the triple-combination mechanical therapy (Merci, angioplasty, and stent) showed neurological improvement (decrease in NIHSS score by ≥4 points). However, the other two patients died from complications related to intracranial hemorrhage.

Future directions for mechanical thrombolysis include new pharmacological agents, better clot disruption techniques or devices, and better clinician understanding of complication...
avoidance. The MicroLysUS infusion catheter (EKOS Corporation, Bothell, WA) is currently undergoing investigation in clinical trials. The unique feature of this device is an ultrasound vibrating tip. By delivering an ultrasonic frequency to the site of the occlusion, this catheter is intended to allow better penetration of the thrombolytic agent and greater dissolution of the clot.

Desmoteplase, a fibrin-specific thrombolytic agent, is currently under investigation in clinical trials. Preliminary data has shown improvement in clinical outcomes after intravenous administration of desmoteplase to patients with perfusion/diffusion mismatch on magnetic resonance imaging scan 3 to 9 hours after ischemic stroke onset. The Desmoteplase in Acute Ischemic Stroke (DIAS) trial and the Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DE-DAS) trial showed higher reperfusion rates and better clinical outcomes at 90 days with desmoteplase compared with placebo.

### TABLE 20.1. Evolution of intra-arterial stroke intervention, University at Buffalo Neurosurgery, State University of New York

<table>
<thead>
<tr>
<th>Year</th>
<th>Urokinase</th>
</tr>
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<tbody>
<tr>
<td>1994</td>
<td>Prourokinase</td>
</tr>
<tr>
<td>1995</td>
<td>Alteplase (tissue plasminogen activator)</td>
</tr>
<tr>
<td>1996</td>
<td>Mechanical clot lysis</td>
</tr>
<tr>
<td>1997</td>
<td>Reteplase</td>
</tr>
<tr>
<td>2000</td>
<td>Abciximab</td>
</tr>
<tr>
<td>2001</td>
<td>Abciximab + low-dose reteplase + low-dose heparin</td>
</tr>
<tr>
<td>2001–2003</td>
<td>Ilb-IIIa inhibitor + reteplase + clot retrieval</td>
</tr>
<tr>
<td>2003–2004</td>
<td>Low-dose heparin + reteplase or urokinase + Ilb-IIIa inhibitor (intra-arterial and intravenous) + clot retrieval</td>
</tr>
<tr>
<td>2004–2005</td>
<td>Merci retriever for failed thrombolytic therapy</td>
</tr>
<tr>
<td>2005–2006</td>
<td>Stent for unsuccessful Merci retrieval</td>
</tr>
</tbody>
</table>

### TREATMENT OF INTRACRANIAL STENOSIS

Intracranial stenosis is associated with up to 10% of strokes and transient ischemic attacks. This rate equals more than 70,000 strokes per year in the United States. Patients who have intracranial stenosis also have a higher rate of cerebrovascular events. Different studies have calculated an annual stroke risk of 10 to 24% among patients with intracranial stenosis who receive medical treatment.

Medical treatment for intracranial stenosis includes aggressive management of risk factors such as hypertension, hypercholesterolemia, and tobacco use. Both aspirin and warfarin have been used for their antithrombotic effects. Retrospective studies suggested that warfarin may be more effective than aspirin. However, the prospective Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial helped clarify the outcomes and indications. WASID was a double-blinded, randomized, multicenter trial consisting of 569 patients. Patients who had symptomatic intracranial stenosis (50–99%) received either warfarin (international normalized ratio, 2.0–3.0) or aspirin (1300 mg daily). Enrollment was stopped after an interim analysis showed that patients within the warfarin group had significantly increased rates of death (4.3 versus 9.7%; \( P = 0.02 \)) and major hemorrhage (3.2 versus 8.35; \( P = 0.01 \)). However, there was not a significant difference in the primary endpoint of ischemic stroke, intracranial hemorrhage, or death from vascular causes (22.1 versus 21.8%; \( P = 0.83 \)). Therefore, warfarin is associated with significantly higher adverse events without added benefit over aspirin.

In the WASID trial, those with symptomatic intracranial stenosis had a 2-year stroke rate of 19.7% when treated with aspirin and 17.2% when treated with warfarin. This high rate of neurological events associated with medical treatment highlights the need for other therapies. Therefore, endovascular interventions have been developed as a means for revascularization. This is analogous to revascularization for cervical carotid artery stenosis. Endovascular treatments for intracranial stenosis have included angioplasty only, predilation followed by balloon-mounted stent placement, primary stent placement, and staged angioplasty with delayed balloon-mounted stent placement. The current technique involves primary angioplasty and/or placement of self-expanding stents.

Considerable knowledge regarding endovascular treatment and stent placement has been acquired from the cardiology experience. However, this is tempered with the understanding that there are major differences between cerebral and coronary vessels. These include significantly less adventitia and elastic tissue within cerebral vessels and relatively greater amounts of smooth muscle cells. Cerebral vessels are surrounded by cerebral spinal fluid, rather than the myocardium that surrounds the coronary vessels. Bone surrounds the petrous cervical and vertebral arteries. Substantially greater deficits result from occlusion of small perforating arteries within the brain than in the heart.

Intracranial angioplasty alone has a complication rate as high as 28%. Risks include vessel dissection, induced vasospasm, distal embolization, and acute occlusion. The recurrent stenosis rates range from 31 to 67% at 3 months. Connors and Wojak refined the “technique with the concept of slow inflation and undersizing of balloons for angioplasty.”

For primary stenting, the risks include plaque dislodgment with resulting shower of embolic debris. “Snowplowing” can occur when loosened plaque is forced into the ostia.
of perforating vessels by the struts of the stent. This can lead to perforating artery strokes.\textsuperscript{9,11,13,15}

A staged treatment approach consisting of minimal angioplasty followed at least 1 month later by stent placement with or without repeated angioplasty was developed to reduce procedural complications.\textsuperscript{12,13} The initial angioplasty minimally dilates the high-grade stenosis. According to Poi- seille’s Law, the flow through a vessel increases by the fourth power of the radius. Consequently, a small increase in luminal diameter will increase blood flow significantly. Therefore, complete recanalization is not necessary. The submaximal dilation minimizes the risk of dissection or embolic shower. Further neointimal proliferation and scar tissue formation, theoretically, provide a protective layer for later stent positioning if needed.

The use of intracranial stents was evaluated in the prospective, multicenter, nonrandomized Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) study.\textsuperscript{20} Symptomatic stenotic lesions (50%) in 61 patients (43 intracranial arteries, 18 extracranial vertebral arteries) were treated with a stainless steel, open-cell, balloon-mounted stent designed for cerebral vessels (Neurolink System; Guidant Corporation, Indianapolis, IN). Results included a 6.6% rate of periprocedure stroke and a 7.3% rate of stroke at 30 days to 1 year after the procedure (one of these four strokes was fatal). The combined 1-year stroke rate of 13.9% compares favorably with the 10 to 24% stroke rate among medically treated patients. Angiographic stenosis of greater than 50% was observed at 6 months in 12 (32.4%) of 37 intracranial stents and 6 (42.9%) of 14 extracranial stents. The stenosis caused symptoms (stroke or transient ischemic attack) in 7 patients (39%). Post-hoc analysis of the data for the 37 patients with intracranial stents revealed that patients with diabetes mellitus, greater postprocedure stenosis, and small pretreatment vessel size, had an increased rate of restenosis.\textsuperscript{20}

Initially, stents designed for the coronary circulation were used in the intracranial circulation. These balloon-mounted stents—even those designed for intracranial use—had significant limitations that included difficulty with navigation through the tortuous intracranial vasculature and the relatively high radial force that was required for stent deployment. These limitations led to the development of self-expanding stents that are specifically designed for intracranial use.

Self-expanding intracranial stents have a greater than 95% successful deployment rate.\textsuperscript{5,21} Self-expanding stents have more flexibility and exert less radial force during deployment. The initial multicenter experience with Wingspan self-expanding stent (Boston Scientific Target, Fremont, CA) treatment of intracranial atheromatous disease was recently reported.\textsuperscript{6} Among 82 lesions treated (78 patients), 5 (6.1%) major periprocedural neurological complications occurred.

With the improved navigation and delivery characteristics of self-expanding stents, the staging of the procedure is generally no longer necessary. In the case of tandem lesions, there is added procedural risk, and staged treatments may be required. In the first procedure, both lesions receive angioplasty, and the more severe lesion is stented with a self-expanding stent.

Future work with intracranial stenting will further explore the results and indications for drug-eluting stents. In one recent trial, eight patients with greater than 70% intracranial stenosis who experienced neurological symptoms despite maximum medical therapy were treated with drug-eluting stents.\textsuperscript{1} Four patients each were treated with sirolimus-eluting or paclitaxel-eluting stents. In this small series, there were no recurrent strokes during an average of 11.1 months of follow up. No restenosis occurred in the five of eight patients who had repeat angiography (mean, 9.6 months). In another recent trial, 18 patients with at least 70% stenosis and/or who failed to improve with medical therapy were treated with drug-eluting stents.\textsuperscript{17} Fourteen patients each received a sirolimus-eluting stent, and four were treated with a paclitaxel-eluting stent. At 1 month, one major stroke was reported. There was no other incidence of major stroke at the 6-month and 1-year periods. No deaths were reported at 1 month, 6 months, and 1 year. There was a single incident of angiographic restenosis during the follow-up period.

The technology and techniques for endovascular treatment of intracranial stenosis continue to improve. Further clinical trials are needed to better define outcomes and indications.

REFERENCES


