STROKE is the third leading cause of death and the leading cause of adult disability in North America, Europe, and Asia (1,2). Intracranial cerebral atherosclerosis accounts for approximately 8 to 10% of all ischemic strokes with a higher reported incidence in the Asian, African, and Hispanic descent populations (3–5). Risk factors include insulin-dependent diabetes mellitus, hypercholesterolemia, hypertension, and cigarette smoking (6–8). In the United States, it is estimated that 40,000 to 60,000 new strokes per year are due to intracranial cerebral atherosclerosis.

INTRACRANIAL ATHEROSCLEROSIS

Etiology

Four mechanisms for ischemic stroke secondary to intracranial atherosclerosis have been proposed: (1) hypoperfusion; (2) thrombosis at the site of stenosis due to plaque rupture, intraplaque hemorrhage, or occlusive plaque growth; (3) thromboembolic events distal to the site of stenosis; or (4) direct occlusion of small penetrating arteries at the site of the plaque (9–14).

Stroke Risk Overview

The annual stroke risk from all causes in patients with intracranial atherosclerosis is estimated to be from at least 3.6% to more than 13% annually (14–20) with the definitive National Institutes of Health (NIH) study demonstrating a first year ischemic stroke rate in the pertinent vascular territory of at least 11% (17).

Review of Studies

Surgical Revascularization — EC/IC Bypass Trial (Extracranial to Intracranial).—In 1985, the EC/IC Bypass Study Group published the results of a trial that attempted to prove benefit for a surgical approach to treating intracranial atherosclerotic stenoses or occlusion (18). This extracranial to intracranial arterial bypass trial was a prospective, multicenter, international study involving 1377 patients and attempted to show that patients with an intracranial atherosclerotic stenosis or occlusion could benefit by an EC/IC bypass. This trial failed for all subgroups, and in particular for those with middle cerebral artery stenosis. There is therefore currently no approved surgical option for the patient population with intracranial arterial stenosis. The EC/IC bypass trial likely failed due to lack of identification of the sub-segment of patients with a hypoperfusion mechanism as the primary and underlying cause for their stroke.

Review of Medical Therapy.—The EC/IC Bypass Study also provided data on the risk of stroke in patients with symptomatic carotid siphon or
middle cerebral artery stenosis or occlusion (18). Patients treated with medical therapy including management of stroke risk factors and aspirin (1300 mg per day) were evaluated as the control arm of this study. A defined subset analysis of the EC/IC Trial data found middle cerebral artery stenoses to have an annual ipsilateral ischemic stroke rate of 7.8% (14).

Thijs and Albers reported on 52 patients with documented symptomatic intracranial stenosis (16). Of these 52 patients, 29 (56%) had a second documented event (transient ischemic attack [TIA] or stroke) while on antithrombotic therapy (warfarin, heparin, or antiplatelet agent). Of these 29 patients that failed medical treatment, 15 (52%) had another treatment failure within a median of 36 days, and 8 of these 15 therapeutic failures were major stroke or death. In summary, out of 52 patients, 8 (15%) had a major stroke or were dead within a median time of 36 days.

The WASID Studies (Warfarin vs. Aspirin for Symptomatic Intracranial Disease).—There have been two studies of medical therapy that evaluated the efficacy and safety of warfarin and aspirin for intracranial atherosclerotic stenosis and thus documented the natural history and attempted to determine “best medical therapy.” The first was a retrospective study of consecutive patients with symptomatic intracranial stenosis evaluated by angiography between 1985 and 1991 at participating institutions (15). Patients with symptomatic intracranial large artery stenosis > 50% treated either with aspirin or warfarin (at the treating physician’s discretion) were evaluated for success of medical therapy (15). During a mean follow-up of 14.7 months in the warfarin-treated group, there was an 8.4% stroke or death rate, and in the aspirin-treated group (mean follow-up 19.3 mo) there was an 18.1% rate of major stroke or death, with 9% stroke in the same vascular territory. In a subset with posterior circulation stenosis, with follow-up of 100 patient years and a mean follow-up of 13.8 months, the annualized stroke rate in the territory of a stenotic basilar artery was 10.7% and in the territory of the vertebral artery it was 7.8%.

Based upon this data, a second pivotal trial was subsequently performed. The multi-center, randomized, double-blind NIH (National Institutes of Health)-sponsored Warfarin-Aspirin Symptomatic Intracranial Disease Trial [WASID]) was performed from 1998 to 2003. It was hypothesized that the optimal antithrombotic therapy for symptomatic intracranial arterial stenosis was uncertain (17). Patients with transient ischemic attack or minor stroke caused by an angiographically verified stenosis of > 50%, of a major intracranial artery and with no other apparent etiology, were randomized to receive either warfarin (INR 2–3) or aspirin (1300 mg/d). The primary endpoint was prevention of stroke and vascular death. The WASID trial was prematurely halted by the NIH on the recommendation of the external Performance and Safety Monitoring Committee “after 569 patients had undergone randomization because of concerns about the safety of the patients who had been assigned to receive warfarin” (17).

These 569 patients (out of a projected 806) were followed for a mean of 1.8 years. In the aspirin treated patients, ischemic stroke in the same vascular territory occurred in one year at the rate of 12%, and in warfarin treated patients at the rate of 11%. Death occurred in 4.3% of patients in the aspirin group, versus 9.7% death in the warfarin group; major hemorrhage was observed in 3.2% of the aspirin group versus 8.3% of the warfarin group; and myocardial infarction or sudden death occurred in 2.9% of the aspirin group versus 7.3% of the warfarin group. Patients in the aspirin group also experienced lower rates of death from vascular causes (3.2% vs. 5.9% respectively), as well as death from non-vascular causes (1.1% vs. 3.8%, respectively). In the mean follow-up period of 1.8 years, ischemic or hemorrhagic stroke or vascular death occurred in 22.1% in the aspirin group versus 21.8% in the warfarin group (17). Because of the very high adverse event rates (stroke and death), high severe hemorrhage rate for patients treated with warfarin, and lack of therapeutic benefit of warfarin over aspirin for prevention of ischemic stroke secondary to intracranial stenosis, the investigators concluded that aspirin should be used in preference to warfarin for patients with intracranial arterial stenosis. However, neither therapy offered acceptable protection from stroke.

INTRACRANIAL ANGIOPLASTY AND STENTING

Over the past two decades, a number of individual reports, and two prospective multicenter trials, have been published regarding intracranial angioplasty and stenting. Patients with symptomatic or asymptomatic, severe intracranial atherosclerotic stenosis who were at high risk for stroke or death were included (22–41).

Literature Review

The earliest reports of balloon angioplasty for intracranial atherosclerosis were reported in the mid 1980s. However, by the late 1990s, the development of improved micro-balloon catheters and smaller balloon expandable stents, initially for coronary applications, lead to an increasing number of reports on revascularization of cerebral blood vessels for intracranial atherosclerosis. In a number of individual series of cases reported, the technical success rates have exceeded > 90%, with clinical complication rates ranging from 0 to 20% (22–38).

Gress et al published the results of intracranial angioplasty in 25 patients for symptomatic vertebrobasilar ischemia in whom medical therapy had failed (30). Angioplasty was effective in reducing the degree of stenosis by > 40% in all 25 vessels. These authors concluded that intracranial angioplasty is effective in the reduction of stenosis and can be performed with relative safety.

In 1999, Marks et al reported upon 23 patients who underwent successful angioplasty for atherosclerotic intracranial stenosis, describing both the immediate and long-term outcomes (40). They reported a 91.3% success rate in decreasing the stenosis and one periprocedural death. Follow-up ranged from 16 to 74 months (mean 35.4 mo) and there was an annual rate of 3.2% for strokes in the territory appropriate to the site of angioplasty.
Connors and Wojak reviewed their 9-year experience of transluminal angioplasty for intracranial atherosclerotic lesions in 70 patients and described an "evolution in technique" (41). In their last 50 patients, they described a slow inflation of an undersized balloon relative to the vessel diameter. Using this technique, they experienced no abrupt vessel occlusions or strokes. Complications included angiographic vessel dissection (14%), vessel thrombosis requiring fibrinolysis (4%), asymptomatic restenosis at follow-up over 3 to 12 months (9%), and one death. Overall, good angiographic and clinical outcomes were achieved in 98%.

Nahser et al published similar results in 20 patients with intracranial vertebrobasilar stenosis. Angioplasty was successful in all cases, with one periprocedural TIA and one stroke, for a 10% procedural complication rate (42).

Gomez et al reported upon 12 patients undergoing elective stenting for symptomatic basilar artery stenosis, with a 100% technical success rate, reduction in stenosis from 71.4% to 10.3%, and no periprocedure complications. Clinical follow-up ranged from 0.5 to 16 months (mean 5.9 mo), with no new strokes or deaths (39).

Yu et al reported the long-term outcomes of endovascular stenting for symptomatic basilar artery stenosis over a four-year period (43). Eighteen patients with recurrent strokes or TIAs presented with a basilar artery stenosis of 79.6% ± 11.7%. These patients underwent successful stenting with a residual stenosis of 7.8% ± 10.9%. There were 11.1% neurological and 5.6% non-neurological hemorrhagic complications, but no deaths. At a mean follow-up of 26.7 months, 83.3% had excellent long-term functional outcome with 55.6% being asymptomatic, although 27.8% experienced several minor episodic symptoms without disability. Only one patient had moderate disability from a recurrent stroke, two patients died from unrelated causes at 30 and 36 months post procedure, and the major disability and death-free survival rate was 67% at 3 years.

In 2005, Marks et al reported the long-term outcomes of 36 patients with 37 symptomatic atherosclerotic intracranial stenotic lesions (44). All patients had neurological symptoms on medical therapy. Clinical and angiographic follow-up was available on 34 patients, ranging from 6 to 128 months (mean 52.9 mo). The mean stenosis decreased from 84.2% to 43.3% after treatment. There were two periprocedural deaths and one minor stroke (periprocedural stroke and death rate 8.3%). Two patients had subsequent strokes in the distribution of the treated lesion; one at 2 months and one at 37 months. The annual stroke rate in the territory of the treated lesion was 3.4% and in the subset of patients with > 50% residual stenosis, it was 4.5%.

The long-term clinical benefit of endovascular therapy for intracranial atherosclerosis is confirmed in the report by Wojak et al (45). The authors reported on 60 consecutive symptomatic patients with intracranial stenoses (all > 70%) who had 67 symptomatic lesions and 4 additional asymptomatic lesions (for a total of 71 lesions), who were treated with a total of 84 procedures over a period of 8 years. Demographics, procedural details, angiographic and procedural results, and long-term clinical and neurological outcomes were analyzed. Angioplasty alone was performed in 62 procedures, while 22 procedures involved intracranial stenting. The overall complication-free procedural success rate was 90.5%. The periprocedural stroke or death rate was 4.8%. Angiographic restenosis occurred in 23 lesions at a mean of 4.6 months; 13 were re-treated without complication. Long-term clinical outcomes were available on all 60 patients: 4 patients died from non-neurological causes. Long-term permanent neurological events included 4 strokes and no neurological deaths over 224 patient-years of follow-up. The annualized stroke rate in the treated vascular territory was 1.8%, the annualized rate of stroke or neurological death was 1.8%, and the annualized stroke and all-cause death rate was 3.0%.

SSYLVIA Trial

The SSYLVIA trial (Stenting of Symptomatic atherosclerotic Lesions in the Vertebral or Intracranial Arteries) was a multi-center, non-randomized, prospective feasibility study, which evaluated the Neurolink intracranial stent system (Guidant Corp: Indianapolis, IN) for treatment of vertebral or intracranial artery stenosis (26). Patients were 18 to 80 years of age, with symptoms attributed to a single target lesion of > 50% stenosis. In 61 patients enrolled, 43 (70.5%) had an intracranial stenosis and 18 (29.5%) had an extracranial vertebral artery stenosis. In the first 30 days, 6.6% had strokes and there was 0% mortality. Successful stent placement was achieved in 58/61 (95%) of cases. At 6 months postprocedure, angiographic re-stenosis of > 50% occurred in 12/37 cases (32.4%) of the intracranial arteries and 6/14 (42.9%) of the extracranial vertebral arteries. Seven (39%) patients had recurrent stenosis and were symptomatic. Four of 55 patients (7.3%) had strokes later than 30 days. Based upon this study, the FDA granted a humanitarian device exemption to treat patients with significant intracranial and extracranial atherosclerotic disease by balloon angioplasty and stent placement.

WINGSPAN Trial

The results of treatment by a combination of balloon dilatation, followed by the deployment of a self-expanding microstent were reported in 15 symptomatic patients with intracranial atherosclerotic stenoses despite medical treatment (46). An anatomically and clinically adequate result was achieved in all patients. The mean initial degree of stenosis was 72%. Balloon dilatation resulted in a mean residual stenosis of 54% which was reduced further to a mean of 38% after stent deployment. All patients were either stable or improved 4 weeks after the treatment. Recurrent TIA did not occur in any patient. An update to this study was presented at the 2005 annual meeting of the American Society of Neuroradiology (47). Forty-five (45) medically refractory patients with recurrent stroke, attributable to intracranial atherosclerotic stenoses > 50% were treated in this prospective, multicenter study and results included an ipsilateral stroke or death rate of 4.4% at 30-days and 7.1% at 6-months.

Use of Drug Eluting Stents

The use of drug eluting stents in small caliber vessels has been devel-
oped to reduce intimal proliferation and subsequent restenosis by locally delivering anti-inflammatory or anti-miticot agents. Two such potential stents tested in cardiac disease are the sirolimus-eluting stent and the paclitaxel-eluting stent. Kirmani and colleagues (48) studied the technical efficacy of drug-eluting stents in 15 patients with intracranial atherosclerotic disease in either the anterior (internal carotid or middle cerebral artery) or posterior (vertebral or basilar artery) circulation. The mean patient age was 57 years and 9 were men. Technical success was achieved in 14 of the 15 patients (94%). The 14 patients treated successfully received the sirolimus-eluting (n = 11) or paclitaxel-eluting (n = 3) stent. No restenosis, new major stroke, or death was observed at 1-month follow-up; 3 patients suffered transient worsening of pre-existing deficits, with complete recovery observed in 2 of the patients at 1-month of follow-up. Of the 5 patients who completed 6 months of follow-up, 1 developed a transient ischemic attack.

This study provides important new data on the application of drug-eluting stents to intracranial cerebrovascular occlusive disease. The investigators have demonstrated the feasibility of using drug-eluting stents for this indication. Further studies are warranted in larger cohorts with longer follow-up periods to fully determine the effectiveness of drug-eluting stents for intracranial arterial stenosis. These stents have the potential to alter the treatment paradigm of interventional neuroradiological procedures, especially for lesions with a high risk of recurrent stenosis.

CURRENT POSITION STATEMENT OF THE ASITN, SIR, AND ASN

(1) For symptomatic patients with a > 50% intracranial stenosis who have failed medical therapy, balloon angioplasty with or without stenting should be considered.

(2) Patients who have an asymptomatic intracranial arterial stenosis should first be counseled regarding optimizing medical therapy. There is insufficient evidence to make definitive recommendations regarding endovascular therapy in asymptomatic patients with severe intracranial atherosclerosis. They should be counseled regarding the nature and extent of their disease, monitored for new neurological symptoms, and have periodic non-invasive imaging at regular intervals of 6 to 12 months (transcranial Doppler, magnetic resonance angiography or computed tomographic angiography) initially, and then by cerebral angiography if warranted. At a minimum, optimal prophylactic medical therapy should be instituted, which might include antiplatelet and/or statin therapy.

(3) Continued evaluation and improvements in both pharmaceutical and catheter-based therapies are needed to reduce the stroke burden from intracranial atherosclerosis.

CONCLUSION

The ASITN, SIR, and ASN concur that sufficient evidence now exists to recommend that intracranial angioplasty with or without stenting should be offered to symptomatic patients with intracranial stenoses who have failed medical therapy. Endovascular interventions are intensive services provided to patients who are at very high-risk for stroke and typically have multiple co-morbidities. Similar to revascularization for extracranial carotid artery stenosis (49), patient benefit from revascularization for symptomatic intracranial arterial stenosis is critically dependent on a low peri-procedural stroke and death rate and should thus be performed by experienced neurointerventionists. We recommend reimbursement by third party insurers so that these patients may have access to such interventions. Continued attempts to improve medical therapy as well as improve the benefits of endovascular therapy are warranted.

References


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