Therapeutic Alternatives for Symptomatic Intracranial Atherosclerotic Disease

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Intracranial Atherosclerosis

Definition of the problem and epidemiology

The importance of intracranial atherosclerosis as a cause of stroke was established by several studies performed in the 1960s [1–3]. In the Joint Study of Extracranial Arterial Occlusion, 3,788 patients with signs and symptoms of ischemic cerebrovascular disease underwent four-vessel angiography [1]. Stenotic lesions were identified in 7.7% of basilar arteries, 6.7% of intracranial carotid arteries, 3.8% of middle cerebral arteries, 3.2% of anterior cerebral arteries, and 2.6% of posterior cerebral arteries. Subsequent studies confirmed that at least 6–10% of ischemic strokes in Caucasians are caused by intracranial stenosis [4,5].

In black, Hispanic and Asian populations the incidence of intracranial large vessel disease is higher. Several studies have suggested that blacks are more prone to develop intracranial large artery atherosclerosis than extracranial carotid artery atherosclerosis or extracranial vertebral artery disease [2,4,6,7].

Risk factors for the development of intracranial stenosis appear to be primarily hypertension and diabetes, but traditional risk factors like smoking are also thought to play a part. Typical intracranial atherosclerotic disease presents primarily in the intracranial carotid artery siphon (usually distal to the ophthalmic artery), the main trunk of the middle cerebral arteries, the distal vertebral artery, the vertebrobasilar junction and the mid-portion of the basilar artery. The annual ipsilateral stroke rate for patients with stenosis at the carotid siphon was 7.6%, and there were no apparent differences in terms of stroke rate in patients whose siphon lesion was asymptomatic or symptomatic [8]. According to the Extracranial/Intracranial Bypass Trial, these rates were similar to the rates of stroke in patients with middle cerebral artery occlusive disease [9]. Moreover, the data on the long-term outcome of patients with angiographically proven basilar occlusive disease are limited and controversial [10–13]. Pessin et al. [11] found a relatively low risk of stroke in patients with symptomatic stenosis of the middle or distal segments of the basilar artery. However, the Warfarin-Aspirin Symptomatic Intracranial Disease study found an annual rate of stroke of 15% in any vascular territory and 11% in the basilar artery territory [13]. Intracranial lesions have a high tendency to produce unheralded strokes, and when those patients have transient ischemic attacks there is a high incidence of subsequent stroke within a short time, usually months [14,15].

Medical management for symptomatic intracranial stenosis

The efficacy of antiplatelet agents has not been established in patients with symptomatic intracranial large vessel disease. In fact, the high rate of stroke in patients with carotid siphon or middle cerebral artery stenosis who were treated with high dose aspirin in the medical arm of the Extracranial/Intracranial Bypass study (7.7–9.5% per patient-year) raises a question about the efficacy of aspirin in this setting [9,10]. The efficacy of newer antiplatelet agents such as ticlopidine and clopidogrel in patients with intracranial stenosis has also not been established.

Warfarin is often used for the treatment of intracranial stenosis based on the results of the WASID study, a non-randomized retrospective study of patients with symptomatic angiographically proven stenosis (50–99%) of a major intracranial artery. Qualifying criteria for the study included: 50–99% stenosis of one of the major intracranial arteries, a transient ischemic attack or minor stroke in the distribution of the stenotic artery, and therapy with aspirin or warfarin. The major findings of this study [13] were twofold: warfarin lowered the combined endpoint of stroke, myocardial infarction or sudden death by nearly 50% compared to aspirin (325 mg/day); and the major benefit of warfarin was in preventing stroke. Warfarin was highly effective in reducing the rate of strokes that occurred outside the vascular distribution affected by the intracranial stenosis, but surprisingly, had little ability to reduce the stroke rate within the distribution of the stenotic vessel. The risk of ipsilateral stroke on warfarin was greater than 5% per year; this observation lends credence to hypoperfusion as a risk for stroke. Several studies have reported transcranial Doppler detection of microembolic signals distally to intracranial stenosis at the acute phase of stroke [16,17], however this was not found in the chronic stage even in those patients who had microembolic signals in the first days after stroke [17,18]. These data suggest that recurrent ischemic events in chronic intracranial stenoses are of hemodynamic origin. Elucidation of the mechanism responsible for cerebral infarction may have clinical implications for tailored treatment for, or prevention of, stroke from intracranial stenosis; for example, warfarin should be investigated as a treatment to prevent artery-to-artery thromboembolism, whereas intervention strategies such as angioplasty and

WASID = Warfarin Aspirin Symptomatic Intracranial Disease study

induced hypertension should be studied to improve perfusion and cerebral hemodynamics [19].

Patients with symptomatic intracranial atherosclerosis who fail antithrombotic therapy appear to be at high risk for subsequent cerebral ischemic events, since recurrent events frequently take place within the first month after failed antithrombotic therapy. Recent data highlight the ill-fated future of patients with intracranial atherosclerotic lesions who fail medical therapy, estimating stroke rates as high as 40–50% within weeks of diagnosis [15]. In the Extracranial/Intracranial Bypass trial, patients with symptomatic middle cerebral artery stenosis randomized to medical therapy had annual ipsilateral stroke rates of 7.8% and total stroke rates of 9.5% [10]. The high recurrent stroke rates may indicate the need for different medical therapies or more aggressive treatment methods such as intracranial angioplasty and stenting.

Surgical management of symptomatic intracranial stenosis

Intracranial bypass surgery (extracranial-intracranial bypass, STA-middle cerebral artery, high flow EC-IC) is also a therapeutic option for patients with intracranial arterial stenosis. However, enthusiasm for bypass has waned since the overall disappointing results of the Extracranial/Intracranial Bypass study were reported [10]. In this study, patients with extracranial carotid occlusion, distal carotid occlusive disease or middle cerebral artery stenosis were randomized to medical therapy alone versus medical therapy and EC-IC bypass. The results of the study showed that EC-IC bypass was ineffective in preventing stroke. Subgroup analyses of patients with distal carotid or middle cerebral artery stenosis also showed that EC-IC bypass was ineffective in these groups.

At the time of the study there were no available means to objectively measure intracranial cerebral blood flow, cerebral metabolism or oxygen demand, and patients with symptoms attributed to thromboembolic occlusions were difficult to distinguish from those suffering from hypoperfusion. Improper patient selection significantly skewed the results of clinical outcomes. To date, the efficacy of bypass and endarterectomy has not been evaluated systematically and recommendations are not definite.

Balloon and stent-assisted angioplasty

Many patients with intracranial atherosclerosis have recurrent cerebral ischemic events despite standard medical therapy with antiplatelets or oral anticoagulants. This subset of patients who "fail antithrombotic therapy" presents a high risk of recurrent stroke and, typically, those events occur within a few months after failure of standard medical therapy [15]. This subgroup of patients represents the ideal group for evaluating the efficacy of intracranial angioplasty versus medical therapy.

Experience in the early 1980s suggested that intracranial angioplasty was associated with an unacceptably high risk of stroke or death, and the procedure was largely abandoned [21,22]. Recent advances in microcatheter and balloon technology have led to renewed interest and use of balloon angioplasty for symptomatic intracranial stenosis [23,24]. Those studies also showed that intracranial angioplasty is technically feasible and may be performed relatively safely. However, rebound stenosis (intrinsic elastic recoil and vessel geometry) and dissection constitute the major weaknesses of balloon-assisted angioplasty and the main reason for considering use of a stent.

With the development and refinement of endovascular stents, the significant potential of these devices in the endovascular treatment of several cerebrovascular conditions such as intracranial aneurysms, atherosclerotic lesions and arterial dissections has become apparent. This versatile device may be essential, acting as a mechanical barrier to prevent coil herniation while treating wide-necked, dissecting and fusiform aneurysms or pseudoaneurysms [25–28]; supporting balloon angioplasty in order to prevent recoiling of the plaque; and covering a plaque or an intimal flap, thereby reducing both emboli occurrence and flap recurrence, respectively [27–29]. The stent may prevent early re-thrombosis after mechanical or pharmacologic successful thrombolysis [28,30].

Flexible microstents can be navigated through the tortuous neurovasculature, accessing distal lesions such as those located at the distal internal carotid, middle cerebral artery, distal vertebral artery, and basilar artery [31–34). The results of intracranial angioplasty have been encouraging; however, most of these series were uncontrolled, and the data on long-term outcomes in patients undergoing intracranial angioplasty are limited. Therefore, the results must be analyzed critically. Intracranial angioplasty should be reserved for those patients at the highest risk who have failed conventional medical therapy.

More reliable prospective multicenter data are needed to determine the role of angioplasty and stenting in the treatment of intracranial stenosis. Ongoing studies such as the WASID trial and the SSYLVIA study (Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries) will provide useful data [35,36]. Thus during the next few years, sufficient prospective data should emerge to enable the design of a large randomized clinical trial comparing best medical therapy versus intracranial stent-assisted angioplasty.

Conclusion

Indications for any therapy depend on both the risks of the untreated disease and the safety and efficacy of the therapeutic procedure. The natural history of intracranial stenoses has not been as well studied as that of extracranial stenoses, but it consistently demonstrates a high rate for stroke. The best antithrombotic therapy has yet to be defined. Since there are no data from randomized clinical trials comparing different antithrombotic agents in this setting, an evidence-based treatment recommendation is lacking. The availability of recently introduced flexible stents, the development of potent antiplatelet inhibitors, and the increasing evidence through experimental and clinical studies support the indication of intracranial angioplasty for high risk patients who failed conventional medical therapy. However, it has not yet been established whether intracranial angioplasty has an acceptable risk/benefit ratio, and its precise role remains to be defined in future studies.

EC-IC = extracranial-intracranial

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