Cervical Arterial Dissection
Time for a Therapeutic Trial?

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Background and Purpose—Cervical arterial dissection is a major cause of stroke in young adults, yet despite standard treatment with anticoagulants or antiplatelet drugs, its management remains uncertain. The goal of this study was to assess the natural history of the disorder and to decide on the feasibility of a therapeutic trial.

Methods—Collaborating members of the Canadian Stroke Consortium prospectively enrolled consecutively referred patients with angiographically proven acute vertebral or carotid arterial dissection. Data recorded included clinical and radiological details, recurrence of ischemic cerebral events, and medical or surgical treatment.

Results—Of 116 patients, 67 had vertebral and 49 had carotid dissections, with no difference in age or sex. In 68 (59%), trauma occurred at the time of dissection. During the course of a 1-year follow-up, at least 17 patients (15%) had recurrent transient ischemic attacks, stroke, or death, mainly in the weeks immediately after the dissection. In 105 patients with complete follow-up, the event rate in those treated with anticoagulants was 8.3% and in those treated with aspirin was 12.4%, a nonsignificant difference of 4.1%. Using these data, we calculate that for a 2-arm trial (aspirin versus anticoagulants) with 80% power and 5% significance, 913 patients are needed in each group.

Conclusions—From our data indicating an initial relatively high recurrence rate, a multicenter trial of anticoagulants versus aspirin involving a total of 2000 patients is feasible. (Stroke. 2003;34:●●●●●●.)

Key Words: dissection • randomized controlled trials • stroke

Cervical arterial dissection is a common cause of ischemic stroke in persons <45 years of age but is a relatively rare cause of ischemic stroke overall. In a recent survey by the Canadian Stroke Consortium (CSC) of ischemic stroke in 356 young adults, dissection accounted for 13% of cases and is likely underdiagnosed.

The incidence of detected carotid artery dissection is estimated to be 2.5 to 3 per 100,000 and vertebral dissection to be 1.5 to 1 per 100,000. The risk of recurrent carotid dissection identified by angiography is ~2% in the first month and 1% annually. Previous studies have focused on recurrence rates of angiographic dissection, with minimal emphasis on recurrence of clinical ischemic events.

Improvements in neurovascular imaging have led to an increased recognition of the role of dissection in stroke and have provided considerable data regarding causation, including genetically determined defects of connective tissue. Despite these advances and numerous case series, no evidence-based guidelines to guide medical or surgical management exist. Most published studies advocating anticoagulant therapy are based on uncontrolled and retrospective data, and no controlled study has yet been undertaken, probably because of the large and uncertain number of patients needed.

Methods and Materials

The CSC is a national network of physicians with a special interest in stroke that over 36 months completed a prospective, multicenter study to assess the natural history of cervical arterial dissection and to determine the feasibility of a therapeutic study. All CSC members were invited to participate. Study data of all dissection patients were collected and reviewed by the data management center in Toronto (Ontario, Canada). Patients >18 years of age with newly diagnosed cervical artery dissection confirmed by conventional angiography (digital subtraction angiography [DSA]), MRI (MR angiography [MRA] and/or MRI), or CT angiography were included. Patients with the typical clinical picture but without radiological confirmation were not included in the study. Study eligibility was verified by the data management center.

The study was approved by the Research and Ethics Board at the study headquarters. A 1-page protocol was completed by local investigators for each patient enrolled, providing clinical details, putative risk factors, family history, methods of neurovascular imaging, and a list of putative risk factors. The study protocol was reviewed by the data management center.

See the Appendix for a list of collaborating members.

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imaging, medical or surgical management, exact details of the time, and circumstances of dissection. In addition, copies of hospital discharge reports, including details of neurovascular imaging, were collected for all patients. Study data were confirmed by review of medical records for all patients, and when data were unclear or incomplete, the investigators were asked for more details. Personal information was encoded to ensure confidentiality.

Cervical arterial dissections were categorized by history of trauma and vascular territory. Dissections were classified as traumatic when there was a history of preceding trauma and as nontraumatic without such a history or when details were unclear. Because classifying trauma into “severe” or “trivial” was an arbitrary decision, we decided against these definitions. Dissection after neck manipulation was included as a subcategory of traumatic and was diagnosed when neck pain (usually with neurological symptoms) occurred within minutes or hours of the manipulation and was confirmed by angiography. Patients with direct or severe trauma such as that from motor vehicle accidents were excluded.

The onset of neurological events after acute dissection was based entirely on patients with head or neck pain because only this well-defined event allowed accurate recollection by the patient. The codings of stroke risk factors (such as hypertension) were left to the discretion of the investigator and were recorded on the study form if the patient had a prior diagnosis or was on medical therapy for the disorder.

The primary outcomes for the study were transient ischemic attack (TIA), stroke, or death. Follow-up assessments were performed for each patient at 6 months and 1 year after enrollment and were completed directly by local investigators or obtained by telephone. In addition to the primary outcomes, Barthel and Rankin disability scores were completed for each patient at 6 months and 1 year. For the analysis, “good” outcomes were defined as Barthel scores >90 and Rankin scores of 0 to 2. All patients had cerebral imaging and vascular imaging to confirm cervical arterial dissection.

Statistical Methods
All data analysis was performed with SPSS, version 10.05 (SPSS Inc). Descriptive statistics were performed for all dissections. Continuous data were summarized as mean±SD or median and range. The frequency of stroke risk factors, time of onset of neurological symptoms, recurrence of clinical events, and outcomes were compared between groups (traumatic versus nontraumatic, carotid versus vertebral); Student’s t tests were used to compare means. When normality and/or equal variance tests failed, the Mann-Whitney rank-sum test was used. Proportional differences between the groups were evaluated with \( \chi^2 \) or Fisher’s exact test. Cox proportional-hazards methods were used to compare treatment groups.

Event rates were calculated as the total number of events by follow-up period in years. “On-treatment” analysis included only events that occurred while a patient was on medical therapy. Survival curves were calculated by the Kaplan-Meier method for time to first event.

Results
Over a 36-month period, 116 patients with cervical arterial dissection were enrolled in the study; of these, 67 (58%) were vertebral and 49 (42%) were carotid. In 2 patients, multiple arteries were involved (Table 1). Fifty-six (48%) were men (mean age, 46±12 years) and 60 (52%) were women (mean age, 42±10 years), a nonsignificant difference. Patients were followed up for an average of 10.0±3.5 months. Eleven patients were lost to follow-up, leaving 105 (90.5%) for analysis.

Clinical Presentation
The most common clinical presentations were stroke or TIA, whereas 9 patients (8%) presented with headache only and 4 (3%) as subarachnoid hemorrhage (Table 2). Horner’s syndrome occurred in 10 patients (20%) with carotid and 7 patients (10%) with vertebral lesions. Wallenberg’s syndrome occurred in 9 patients (13%) with vertebral dissections. One patient with upper cervical spontaneous carotid dissection and 3 with vertebral dissections had subarachnoid hemorrhage. One patient with anisocoria was noted to have a small pupil by her observant husband after she had moved some heavy furniture. Angiography confirmed an ipsilateral carotid artery dissection. She remained neurologically asymptomatic.

Headache or neck pain occurred in 86 of 116 patients (74%), more commonly with vertebral (57 of 67, 85%) than with carotid (29 of 49, 59%) dissection (P<0.001), and the exact onset could be determined in 77 patients from this finding. In 54 of 77 patients (70%), symptoms occurred within 24 hours; in 14 of 77 (18%), within 1 week; and the remainder (12%), within 2 months. The time of onset of neurological events after the onset of pain did not differ in the 2 arterial groups.

Risk Factors for Dissection
Two risk factors for dissection became evident in this study, trauma and connective tissue disorders. Traumatic dissections were more frequent than nontraumatic dissections (59% versus 42%, P=0.013). Dissection after neck manipulation was observed in 20 patients (17%; 19 chiropractic, 1 physiotherapeutic), and none of these had clinical or angiographic evidence of congenital arteriopathy.

Connective tissue disorders were identified in 21 of 116 patients (18%). Fibromuscular dysplasia was diagnosed angiographically in 19 patients and clinically in 2 patients (Marfan’s syndrome and Ehlers-Danlos type IV). These abnormalities were distributed equally between the carotid and vertebral groups but were significantly more frequent in patients with nontraumatic compared with traumatic dissections (P=0.0211).

The frequency of stroke risk factors in this study resembled the rates in the general population, as documented in other large cohort studies.4-10 These risk factors were as follows: smoking (23, 20%), hypertension (21, 18%), migraine (15,
Neurovascular Imaging
Neuroimaging was performed as part of the initial evaluation in all patients. Overall, most patients (80%) had CT scanning of the brain, followed by DSA, MRA, MRI, and duplex ultrasound. DSA was the most common neuroimaging method (70%) for confirmation of dissection. The most common abnormality identified was irregularity of the lumen (38%), followed by a “rat’s tail” stenosis (28%) and complete occlusion (28%). Pseudoaneurysms were seen in 6 patients (5%). Dissections were purely extracranial in 105 (90%), extracranial with intracranial extension in 8 (7%), and purely intracranial in 3 (3%). Intracranial dissections were all vertebral.

Ischemic infarction was identified in 104 patients (90%), most often in the cortical region, and then in the brain stem and cerebellum or other subcortical areas. In addition, 4 patients (3%) had subarachnoid hemorrhages.

Medical and Surgical Treatment
Management was decided by the individual investigators. All patients received some form of medical therapy, including anticoagulants in most (78 patients, 67%), followed by antiplatelet agents in 23 (20%) and both drugs in 5 (4%). Treatment was typically initiated with anticoagulants and changed to antiplatelet agents after 4 to 12 weeks. Three patients with carotid dissection received intravenous tissue plasminogen activator, resulting in recanalization in 1 patient. No patient receiving thrombolytic therapy had any hemorrhagic complications or evidence of a new dissection. Two patients with vertebral dissection had stents inserted.

Outcome and Recurrence
Complete follow-up data were available for 105 of 116 patients (90%) enrolled in the study. Most had a good outcome at 1 year, 93 (89%) with a Rankin scale of 0 to 2 and 90 (86%) with a Barthel score >90.

Overall, a total of 17 patients (15%) had recurrent events, 8 before and 9 after enrollment in the study. Before enrollment, 5 patients had further strokes and 3 had further TIs. These events were not included in the final analysis because details of drug therapy were uncertain. After enrollment, 9 patients had further events: 4 nonfatal strokes, 2 TIs, and 3 deaths. Most of these events occurred in the first 2 weeks after dissection (the Figure).

The annual event rate in the postenrollment group was 10.4% per year (9 of 105; Table 3). The rate of recurrence was higher in the aspirin-treated (12.4%) than anticoagulant-treated (8.3%) patients (Cox proportional hazards: hazard ratio, 1.50; 95% confidence interval, 0.3 to 7.8; P=0.63). Hypertension was more common among individuals with recurrence compared with those without recurrence (P<0.04), but the other putative risk factors were not significantly different.

Discussion
Over a 36-month period, we identified 116 patients with cervical arterial dissection in Canada, an underestimated rate because not all centers participated. Vertebral artery dissection was more common than carotid dissection, and most patients presented with headache and cerebral ischemia. All patients received medical therapy, with anticoagulants prescribed most often. However, mounting evidence, such as in the Warfarin Versus Aspirin for Secondary Stroke Prevention (WARSS) trial,11 suggests that anticoagulants are no more effective than antiplatelet drugs in preventing further ischemic events after strokes of arterial origin. Conversely, most recurrent events after dissection are probably thromboembolic, arising from fresh arterial tears,12 and differ from the underlying pathology in WARSS patients with predominantly chronic atherosclerotic lesions. Evidence of the thromboembolic potential of dissection comes from various sources. Transcranial Doppler detects cerebral microemboli in 46% to 59% of patients monitored in the immediate postdissection period and may predict future ischemic events.13,14 Also, the cortical distribution of infarcts after dissection suggests an embolic pattern.15

The primary finding of this study was a surprisingly high annual recurrence rate of 10.4%, and those treated with anticoagulants had fewer recurrent events than patients treated with antiplatelet agents. Prospective enrollment of patients facilitated more accurate documentation of clinical events occurring during the patient’s hospitalization than possible in retrospective surveys in which data often are

| TABLE 3. Annual Event Rate in 105 Treated Patients With Recurrent Events |
|-----------------------------|------------------|-----------------|-----------------|------------------|
|                             | Anticoagulant    | Aspirin         | Other           | Total            |
|                             | (n=71)           | (n=23)          | (n=11)          | (n=105)          |
| Follow-up, y                | 6.0 (1.6)        | 16.1 (4.7)      | 9.5 (2.3)       | 86.3 (24.6)      |
| TIA, n                      | 1                | 1               | 0               | 2                |
| Stroke, n                   | 2                | 1               | 1               | 4                |
| Death, n                    | 2                | 0               | 1               | 3                |
| Total, n                    | 5                | 2               | 2               | 9                |
| Event rate per year, %      | 8.3 (2.3)        | 12.4 (3.5)      | 21 (5.3)        | 10.4 (3.1)       |

Other indicates combination of aspirin and anticoagulants or stents. Follow-up is in total patient-years. 
collected long after hospital discharge. This finding is critical for calculating numbers for a clinical trial. In a recently published study of carotid dissection, patients had much lower annual recurrence rates: 1.4% in those with permanent arterial stenosis or occlusion and only 0.6% in those with transient occlusion.\(^{10}\) However, follow-up, by telephone or clinically, was 1 year after symptom onset, so ischemic events in the acute period could easily have been missed or forgotten. Other major limitations of this study, involving 92 patients, were the low number of examined patients and the reliance on ultrasound alone to diagnose the arterial lesions.

The hallmark of dissection is neck pain or headache (74% in our study), often severe\(^{16}\) and allowing accurate timing of the moment of dissection. Our data indicate that most (70%) neurological events follow arterial dissection within 24 hours but may be delayed for as long as 2 months, long after the traumatic event could be forgotten, which has critical implications for both diagnosis and treatment. Ischemic stroke occurring up to 2 months after neck trauma and attributed to dissection has been documented by autopsy.\(^{17,18}\) This observation also has important medicolegal implications.

Although DSA was the most commonly used imaging modality, MRA is now almost as accurate in both initial diagnosis and follow-up and, with the addition of MRI cross-sectional imaging of the arteries, can effectively replace catheter angiography.\(^{19,20}\) However, the infrequent use (27%) of ultrasound examinations by neurologists in this study reflects skepticism about its diagnostic value, not shared universally.\(^{21}\)

Three patients, all with carotid dissection, had intravenous tissue plasminogen activator therapy, resulting in complete recanalization in 1 patient, without complications. Although thrombolytic therapy, both intravenous and intra-arterial, is increasingly used in acute dissection, usually without significant complications or evidence of extension of the lesion, it remains an empirical and unproven therapy.\(^{22,23}\)

Surgical intervention was rarely used in this study; 2 carotid stents were inserted without complication. Angioplasty and stenting have been reported,\(^{24}\) but this procedure is risky, and there are no consensus guidelines. Because most dissections heal uneventfully and associated aneurysms never rupture, arterial grafting or extracranial-intracranial bypass is indicated only in patients refractory to medical therapy or unsuitable for endovascular procedures.\(^{14}\)

**Calculations for a Therapeutic Trial**

Comparisons of other antiplatelet and anticoagulant stroke prevention trials with our data are difficult because the underlying pathology in dissection is unique. The abrupt intimal tear immediately attracts thrombus, explaining the high immediate rate of recurrent events, but once the injury heals, recurrence is rare. This is fundamentally different from the mechanism of embolism arising from chronic, ulcerated arterial plaques or cardiac sources. In addition, for trial calculations, recurrent, asymptomatic dissections observed on angiography\(^4\) cannot be equated with recurrent clinical events.

In antiplatelet trials, the annual recurrence rate of stroke in the placebo arms is \(\approx 8\%\), whereas in the aspirin-treated groups, this rate is reduced to 5% to 6%,\(^{25-27}\) an absolute risk reduction of only 2% to 3% and a relative risk reduction of 25%. Similarly, in meta-analyses involving thousands of patients, the relative risk reduction with aspirin in secondary prevention of “arterial” stroke is estimated to be \(\approx 13\%\) to 25%.\(^{28,29}\)

However, risk reduction in the secondary prevention of ischemic events in patients with atrial fibrillation is significantly better with oral anticoagulants, with a 15% per year stroke rate in the aspirin group versus 8% per year in the anticoagulant group.\(^{30}\) Results of other stroke prevention trials comparing anticoagulant and antiplatelet agents vary, depending on the cause. In general, the absolute risk reduction is superior with anticoagulants compared with antiplatelet drugs by 1.8% to 11%, as in an intracranial arterial stenosis trial (Warfarin-Aspirin Symptomatic Intracranial Disease [WASID]),\(^{31}\) an arterial ischemic stroke trial (Stroke Prevention in Reversible Ischemic Trial [SPRIT]),\(^{32}\) and the Stroke Anticoagulant Trial.\(^{33}\)

To calculate the effect of treatment on recurrence in our study, using the event rates in the 9 patients treated after enrollment (4 strokes, 3 deaths, and 2 TIAs.), we found that the difference in annual event rates between aspirin (12.4%) and anticoagulants (8.3%) was 4.1% (not significant). From these data, we calculated target sample sizes for a standard 2-arm trial with 80% power and 5% significance as 913 patients in each group. This resembles the Cochrane meta-analysis calculation of 945,\(^8\) with an estimated annual event rate on anticoagulant treatment of 15% and on antiplatelets of 20%, an absolute difference of 5% (similar to our study). In most large metropolitan hospitals, \(\approx 10\) to 12 patients with cervical arterial dissection are seen annually, so a 5-year trial involving about 50 centers would enroll 2000 patients, allowing for a 20% failure of enrollment.

During the course of this study, we were aware that many cervical arterial dissections were diagnosed elsewhere by physicians not participating in our study and thus were not referred to us. In addition to the general lack of awareness by the medical community of the role of dissection as a cause of stroke, this suggests that many more patients were affected than were enrolled. It is probable that more patients would be enrolled in a more formal and structured prospective study.

Because of low numbers, event rates are low and calculations are susceptible to type I error, so a preliminary model based on this study and initially consisting of 10 centers might be advisable to decide on the logistics of recruitment before a major multicenter study is begun.

Because for ethical reasons a placebo arm is not feasible, a randomized trial of anticoagulants versus low-dose aspirin would probably be the only practical strategy. In our study, most recurrent ischemic events (including TIAs) occurred in the first 30 days, so there would be no need to expose patients to the hazards of major hemorrhage in the anticoagulant group more than at most 90 days, thereafter continuing both trial groups on aspirin for 6 to 12 months.

In conclusion, from our preliminary observations and with a large-enough cohort of patients, the question of whether anticoagulants are better than aspirin in the prevention of
recurrent events after cervical arterial dissection can be answered.

Appendix

List of Collaborators

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