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Review Article

Cervical artery dissection: Pathology, epidemiology and management

Yang-Ki Kim [a,b], Sam Schulman [a,*]

[a] Department of Medicine, McMaster University, Hamilton ON, Canada
[b] Department of Medicine, Soonchunhyang University, Seoul, Korea

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ABSTRACT

Background: Cervical artery dissection is often treated with anticoagulants to prevent ischemic stroke. The risk-benefit ratio of anticoagulation versus antiplatelet therapy is unclear.
Objectives: To provide an educational review of current data on the disease to explain the rationale for the treatment options and to explore the results of management studies in order to determine if anticoagulation is justified.
Methods: We searched the databases MEDLINE and EMBASE as well as bibliographies for information on anticoagulants and antiplatelet agents in cervical, i.e. carotid and/or vertebral artery, dissection.
Results: There are no randomized controlled trials on the treatment. One systematic review from 2003 identified 20 case series or cohort studies. We identified 9 additional studies with a total of 1,033 patients. Of those, 731 received anticoagulation sometimes followed by platelet inhibition vs. 282 patients treated with antiplatelet agents alone. The rate of ischemic stroke was 2.3% vs. 6.9% and bleeding complications were reported in 0.7% vs. 0%.
Conclusion: It cannot be excluded that there is a net benefit from anticoagulant therapy in cervical dissection, but the studies are flawed by considerable bias. Very ill patients at a high risk of ischemic stroke may have been given aspirin due to fear of hemorrhagic complications. A randomized controlled trial is planned and will be crucial to resolve this issue.

Contents

Abbreviations: CAD, cervical artery dissection; ICAD, internal carotid artery dissection; VAD, vertebral artery dissection; TIA, transitory ischemic attack; hsCRP, high-sensitivity C-reactive protein; MTHFR, methylene-tetrahydrofolate reductase; AT, α1-antitrypsin; FMD, fibromuscular dysplasia; MRI, magnetic resonance imaging; CT, computed tomography; SAH, subarachnoid hemorrhage; MRA, magnetic resonance angiography; CTA, computed tomographic angiography; CDS, color duplex ultrasound; PPV, positive predictive value; NPV, negative predictive value; MES, microembolic signal; rtPA, recombinant tissue plasminogen activator; INR, international normalized ratio; IAD, intracranial arterial dissection; NIHSS, National Institutes of Health Stroke Scale; CADISP, Cervical Artery Dissection in Ischemic Stroke Patients; mRs, modified Rankin score; OR, odds ratio; CI, confidence interval.

* Corresponding author. Thrombosis Service, HHS-General Hospital, 237 Barton Street East, Hamilton ON, Canada L8L 2X2. Tel.: +1 905 5270271; fax: +1 905 5211551.
E-mail address: schulms@mcmaster.ca (S. Schulman).

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Introduction

Cervical artery dissection (CAD), i.e. internal carotid artery dissection (ICAD) and/or vertebral artery dissection (VAD), has an annual incidence of 2.6–3.0 per 100,000 [1,2]. The spontaneous dissection of the carotid or vertebral artery accounts for only about 2 percent of all ischemic strokes, but for 10 to 25 percent of such events in young and middle-aged patients [2–4].

The management consists of a combination of strategies including anticoagulants, platelet aggregation inhibitors, thrombolytic agents, endovascular stent angioplasty, or surgery. Although 70-86% of patients with ICAD and 90-96% of patients with VAD present with ischemic events, namely ischemic stroke and transitory ischemic attack (TIA), as initial clinical manifestation and the main mechanism is embolic rather than hemodynamic, a randomized trial of antithrombotic treatment has never been reported. This review focuses on etiology, pathogenesis, and comparisons between anticoagulants and platelet aggregation inhibitors in CAD [1,5,6]. A recent review by Redekop on the same topic focused on extracranial dissections and discussed more in depth the role of major blunt trauma [7]. That review also presented indirect evidence that early antithrombotic treatment in general appears to reduce the risk of stroke compared to no treatment. In our review the comparison of antiplatelet and anticoagulant therapy is further developed and we have also focused more on pathogenesis and risk factors to illustrate the mechanisms of disease that may provide a rationale for a specific treatment.

Method

Using the computerized search of MEDLINE database (1961 to April, 2008) and EMBASE (1980 to April, 2008) we retrieved articles published in English by using the following MeSH terms and text words: “internal carotid artery dissection”, “vertebral artery dissection”, “cervical artery dissection”, “anticoagulants”, “heparin”, “low-molecular-weight heparin”, “platelet aggregation inhibitors”, “aspirin”. In order to avoid duplication of data, we set criteria for inclusion of articles as those never used in meta-analysis and never reported as different topics in the same population. We reviewed the bibliographies of articles retrieved through the search for additional relevant articles. We retrieved 808 articles on the subject.

Definition and Classification

Cervical arterial dissection is defined as the splitting of the arterial wall of the carotid or vertebral artery. It is further classified as intracranial or extracranial artery dissection. The prevalence of extracranial artery dissection is more frequent than intracranial since the latter represents only 10-40% of CAD [6,8,9].

Pathogenesis

The extracranial portions of internal carotid and vertebral arteries are more vulnerable to dissection than their intracranial segments despite their similar size [10,11]. The vulnerability of the extracranial portion of the internal carotid artery has been explained by the fact that it is freely movable on the neck and its fixation at the entry into the carotid canal at the base of skull makes it susceptible to strain. In addition, the proximity of the carotid artery to the anterior surface of the upper cervical vertebrae contributes to its exposure for injury. The vulnerability of the extracranial portion of the vertebral artery to strain and sudden neck movement has been explained by the fact that it has high mobility when passing through the transverse foramina of cervical spines, as well as the change of direction from vertical to horizontal at the level of the first cervical vertebra, after which the artery becomes fixed [10].

Once a tear occurs in the wall of major arteries of the neck, blood is allowed to enter between the layers of the wall of the artery, forming an intramural hematoma. The splitting of the layers caused by an intramural hematoma results in either stenosis, when the intramural hematoma is formed between the intima and media, or aneurysmal dilatation, when the intramural hematoma is located between the media and adventitia [11]. As another suggested mechanism, intramural hemorrhage forms through ruptures of the vasa vasorum [12,13] without intimal tear, especially if the wall is arteriopathic [14].

It has repeatedly been suggested that underlying arteriopathy plays a role in the pathogenesis of spontaneous CAD. To study the connection between spontaneous CAD and connective tissue abnormalities, 25 patients diagnosed with the former without hereditary connective tissue disorder had dermal connective tissue analyzed with transmission electron microscopy. Abnormalities of collagen and elastic fibers within reticular dermis were identified in 17 (68%) of the patients with CAD, but were not present in any of the 10 controls ($p = 0.0003$), and the findings resembled those seen mainly in Ehlers-Danlos syndrome type III [15]. Based on the fact that skin plays the role of a window to hereditary diseases of the connective tissue [16], it was suggested that the systemic alterations in connective tissue components might be associated with weakness of the vessel wall causing spontaneous CAD [15,17]. This was supported by a study in which biopsy of the superficial temporal artery was obtained in 9 patients with spontaneous CAD [14]. A zone at the junction between the tunica media and the tunica adventitia had weakened with fissuring in 7 of 9 biopsy specimens, but not in any of the controls. Patients with spontaneous CAD may thus suffer from a generalized arteriopathy and reduced stability of the arterial wall [14].

Another question is whether an inflammatory mechanism is involved in the pathogenesis of arterial dissection. High-sensitivity C-reactive protein (hsCRP) is a pro-inflammatory marker and contributes to endothelial dysfunction through effects on vessel wall [18]. Sixty-two consecutive patients who suffered from ischemic stroke or TIA 9 to 24 months before study entry were classified as having large artery atherosclerosis (n = 21), non-traumatic CAD (n = 21), or cryptogenic embolism (n = 20), and were compared with a control group with age-matched volunteers without known vascular disease (n = 54). After adjustment for confounding variables, only CAD was associated with elevated hsCRP (odds ratio 7.9 [1.8 to 34]; $p = 0.004$). The authors assumed that the hsCRP level obtained so far from the event reflected the inflammatory response before the ischemic event and postulated that an inflammatory mechanism is involved in the development of CAD [18] since that response generally is considered to last for a maximum of 3 months after a stroke [19].