Carotid Artery Restenosis in a Hispanic Population

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***Background* and *Purpose*: Carotid endarterectomy is one of the main surgical procedures used for carotid stenosis and its recurrence. Besides the setting of a randomized controlled trial for asymptomatic and symptomatic carotid artery stenosis, there is little information about the rate of restenosis after carotid endarterectomy in Hispanics. The purpose of this study is to describe the results of carotid endarterectomy on the basis of restenosis in a Hispanic population.**

***Method*: A retrospective revision of 47 endarterectomies performed on 43 patients by a single surgeon at the VA Caribbean Health Care System and Pavía Hospital, during an eight year period (1990-1998), was conducted. Information about endarterectomies, restenosis and known risk factors for carotid stenosis were obtained from medical records.**

***Results*: Of the 43 patients, 31 were male (72%) and 12 female (28%), with a mean age of 67.9 years. Re-operations for recurrent carotid stenosis were performed in 2 patients (4.7%). Restenosis cases were asymptomatic, hence diagnosed through follow-up ultrasound Duplex studies and confirmed by angiography after 3 and 4 years of the first surgical procedure. The degree of restenosis (70% to 99%) after the initial endarterectomy was 4.3%. The major risk factors found among patients were hypertension (58%), hypercholesterolemia (50%), smoking (46%), and alcohol (34%).**

***Conclusions*: Carotid endarterectomy with primary closure is safe and durable. Repeated surgery using patch grafts in this Hispanic population was also safe. The concordance of risk factors and incidence of carotid stenosis correlated well with other studies.**

Key words: Carotid Artery Stenosis, Endarterectomy, Hispanics, Restenosis

Stroke is a preventable disease. Cerebrovascular events remain the third leading cause of deaths in industrialized countries (1). Epidemiologic studies have identified race, sex, and age as risk factors for stroke (1). The age is the most powerful predictor of stroke; hence incidence rises exponentially with advancing years (1). Another relevant factor is systemic blood pressure. Hypertension is the most important risk factor of hemorrhagic strokes, as cited by the Framingham study (2). Blood pressure over 160/95 increased the age adjusted relative risk for stroke by 31% for men and 29% for women, even in the elderly. It is estimated that about 40% of strokes are due to a systolic blood pressure over 140 mmHg (3). Atherosclerosis is also the most noteworthy pathology causing transient ischemic attacks (TIA) and strokes in high-risk populations (3). Due to the pathology of the disease, atherosclerosis is the principal cause of extracranial carotid stenosis and also a significant factor in restenosis after endarterectomy (4). Other known risk factors related to the pathology involved in carotid stenosis, restenosis and strokes are hemodynamic forces, diabetes mellitus, life style, and diet.

Several studies have demonstrated that carotid endarterectomy (CEA) is a safe procedure that reduces the risk of stroke in patients with asymptomatic and symptomatic carotid stenosis. However, the benefit of CEA is very dependant on the surgical risks corresponding to the patient's comorbidities and on surgical expertise. Randomized controlled trials like the MRC European Carotid Surgery Trial (ECST) and the North America Symptomatic Carotid Endarterectomy Trial (NASCET), published in 1991, studied carotid endarterectomy in symptomatic patients (5-10). The purpose was to evaluate the risk and benefits of CEA in patients with ipsilateral arterial occlusion after a recent non-disabling ischemic stroke, transient ischemic attack, or retinal infarct. Both studies investigated the degree of carotid stenosis above which surgery is beneficial and below which is harmful. ECST initially defined the different degrees of internal carotid artery stenosis as mild (0-29%), moderate (30-69%), and severe (70-99%). After several publications and long-term follow-up, ECST concluded that surgery is beneficial in patients with severe (70-99%) stenosis, harmful in mild stenosis cases, and indicated for few selected patients with moderate stenosis (those

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approaching 70% stenosis). In the Asymptomatic Carotid Atherosclerosis Study (ACAS), elective CEA was demonstrated to have a reduced 5-year risk of ipsilateral stroke for patients with asymptomatic pathology if there was less than 3% perioperative morbidity and mortality and aggressive management of modifiable risk factors. Surgery was indicated for a stenosis greater than 60% in patients with adequate general health (11).

Due to the surge of less invasive procedures like carotid angioplasty and stenting (CAS), CEA risks and durability has been challenged (12). Angioplasty with stenting provides another alternative treatment modality for carotid stenosis. Plaque fragmentation and restenosis can be reduced with stent placement. Angioplasty and stenting is particularly helpful in certain types of stenosis as post-endarterectomy, post-radiation, vascular fibromuscular dysplasia or high cervical carotid stenosis in patients with a high risk for myocardial infarcts during general anesthesia (12-14). The main risk of CAS is stroke. During the procedure, an embolus can be released from the vessel walls or from the catheter system. Several new devices have been designed to trap any debris dislodged during the procedure. Another mechanism of stroke during CAS is during dilatation of the atherosclerotic artery, which could cause breaking of the plaque, causing a decrease in the luminal diameter or dissection of the vessel wall. Restenosis after CAE and CAS has been reported (12-13). Post-CAS restenosis is believed to be due to a combination of elastic recoil and neo-intimal proliferation at the angioplasty or stent site (12). It is important to analyze the incidence of restenosis after CAE and CAS, because if this parameter is different for these procedures, it could make one preferred over the other.

Recurrent carotid stenosis is a long term complication of carotid endarterectomy, aside from inadequate surgical technique, it has been difficult to identify risk factors, although it is believed that continuation of smoking habits and persistence of systemic diseases like hypertension, diabetes mellitus, and hypercholesterolemia are factors that predispose to the restenosis pathophysiology (15). This series of recurrent carotid disease presents the experience of a Hispanic population with similar risk factors.

The risk of non-fatal strokes in high-risk patients treated with platelet anti-aggregants was associated with a reduction of adverse vascular events. A variety of platelet anti-aggregants has been studied for patients with cerebrovascular disease like a low aspirin dose, blocking of platelet cyclooxygenase, and combination with dipyridamole that has demonstrated to enhance the reduction of additional ischemic cerebral events (12, 14). Another platelet antia-ggregant that has been studied for patients with cerebrovascular disease is ticlopidine hydrochloride that blocks adenosine diphosphate without an effect on cyclooxigenase. Ticlopidine in comparison with placebo significantly reduced the annual rate of myocardial infarct, stroke, and vascular death (16). This drug has shown a lower incidence of gastrointestinal hemorrhage, but diarrhea and neutropenia are frequent side effects. Another medication frequently used as a platelet anti-aggregant is clopidogrel bisulfate. Clopidogrel bisulfate is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. However, there is no evidence to support the prevention of restenosis with the use of these drugs (17).

Recent investigations have determined gender as a primary predictor of outcomes after carotid endarterectomy (18). Even though men are more prone to stroke than women in all age groups, except for the most elderly, investigations have shown that women are at higher risk for a postoperative TIA or stroke. The surgical technique used for the closure of the arteriotomy incision has been related to carotid recurrent stenosis. The arteriotomy incision can be primary closed by suturing the artery incision borders back together, or using a patch or graft. The patch can be sutured to the arteriotomy borders increasing the diameter of the vessel. The patch material consists of vein or synthetic material. Primary closure (non-grafting) technique during CEA and female gender seems to confer a higher risk for early restenosis (18). Similar factors have been identified when late recurrences are considered. At an average of 35 months follow-up, Ricottwa et al, noted an association of recurrent stenosis with female gender, age younger than 60, primary closure, and absence of diabetes mellitus (19). However, the usefulness of patch angioplasty at initial endarterectomy for primary operations or reoperation remains controversial (19-20).

Carotid artery restenosis (excluding residual lesions) has been reported with an incidence of 1% to 37% (21). The differences on these incidences can be explained based on the methods of assessment, length of follow-up, and definition for restenosis. The earliest studies were based on angiography; now Duplex ultrasound is 90% reliable, noninvasive, and good for the initial diagnosis and subsequent follow-up after surgery. With the use of Duplex scan ultrasound, some recent literature report incidences of restenosis of about 19% at 16 months, or as high as 37% in a follow-up series of a seven year period (22).

Subjects and Methods

The medical records of 216 patients that underwent carotid endarterectomies at the San Juan Veteran Affairs Hospital and Pavia Hospital, operated by a single surgeon during eight years (1990-1998), were reviewed retrospectively. The records that documented at least five years of clinical follow-up after the endarterectomy, with at least one yearly Duplex scan ultrasound study were selected for analysis. The medical records of 43 patients that had undergone 47 endarterectomies procedures (4 patients had undergone bilateral carotid endarterectomies) were studied. The average age of the patients was 67.9 years old and an average weight of 164 pounds. Thirty-one patients were men and twelve were women. Subjects underwent neurological examination and were screened for carotid restenosis with a Duplex Scan Ultrasound at least once a year. Patient records were analyzed for restenosis and known risk factors for carotid artery stenosis.

Patient follow-up studies were based on Duplex scan ultrasound. Carotid extracranial stenosis and restenosis were defined when the common or internal carotid artery had a peak systolic velocity greater than or equal to 2.00 m/s, suggestive of a >70% stenosis. Conventional cerebral angiography was performed in every patient prior to the endarterectomy. Head CT scan was also utilized selectively prior to surgery for the diagnosis of either ischemic or hemorrhagic infarcts, 26 were done with sixteen scans (61%) showing evidence of lacunar infarcts or brain regional infarcts. MRI and MRA were also done in a few patients. The Duplex scan was done routinely every six to twelve months for five years, and if restenosis was suggested by this test, it was further confirmed with cerebral angiography. Angiography was also used to document intracranial circulation peculiarities and surgical planning. Pre-operative and post-surgical symptoms like transient ischemic attacks, strokes, headaches, and amaurosis fugax were evaluated; however, the study focused on the incidence of carotid artery restenosis based on Duplex studies and confirmed by angiography.

Results

In this series, 43 patients underwent 47 endarterectomies at the VA Caribbean Health Care System and Pavía Hospital, from 1990 to 1998, and had at least one yearly Duplex scan ultrasound follow-up study. The incidence of the known risk factors for carotid stenosis in this study population were hypertension 58%, hypercholesterolemia 50% (with a total blood cholesterol average of 224 mg/dL), smoking 46%, diabetes mellitus 44%, alcohol use 34%, overweight/obesity 42%, and family history of cerebro-cardiovascular diseases 28%. (Figure 1) In terms of the pre-operative symptomatology, 57% of the patients presented transient ischemic attacks (TIA) or Amaurosis Fugax, 39% mild non-disabling stroke, 32% had headaches, and in 4% of the evaluated patients the stenosis was an incidental finding (Figure 2). Cervico-cerebral angiograms were performed in all patients prior to surgery, showing 50-99% stenosis in 56% of the patients, and a complex plaque (50-99% stenosis with an ulcerated plaque) in 44%.

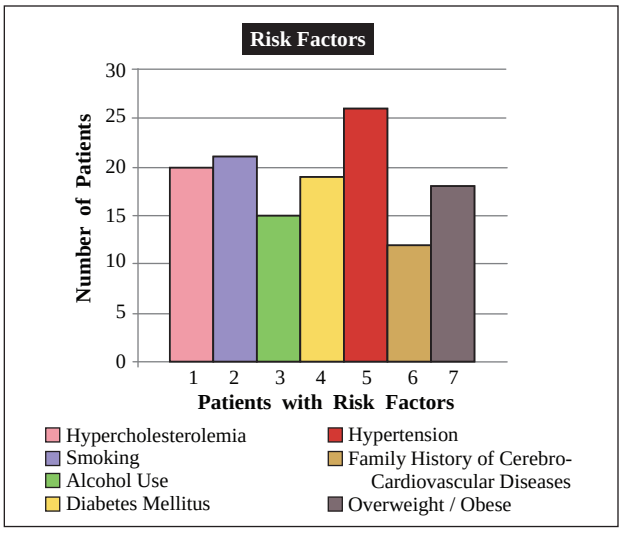

Figure 1. Distribution of risk factors within the studied Hispanic population. Hypertension was the predominant risk factor followed by hypercholesterolemia and smoking.

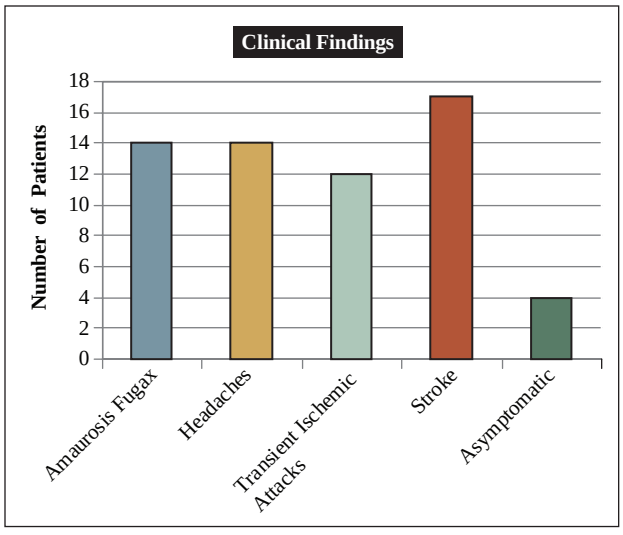

Figure 2. Selected clinical pre-operatory findings and distribution within the studied population with carotid artery stenosis.

Endarterectomies were primarily closed (not using a patch graft) in the initial procedure. Only three minor complications were reported after the initial endarterectomy, a wound hematoma, one transient hypoglossal weakness, and a superficial wound infection. Javist shunts were also used in five patients (10.6%); the mean carotid artery occlusion time was 24.4 min overall. After the initial CAE, the patients were encouraged to modify life style risk factors, and platelets anti-aggregants were prescribed after surgery.

Two completely asymptomatic patients were identified with carotid restenosis in the post-operative period. These two patients were taking aspirin at the time of the diagnosis. Duplex scan identified the restenosis after 3 and 4 years of the initial CAE, respectively. The restenosis was confirmed by cerebral angiogram. The postendarterectomy incidence of angiographically confirmed restenosis of 70% to 99% was 4.3% in this series. These two patients underwent repeated CAE successfully. Although a detailed follow-up of the original non-studied 173 patients is not available, no other patients from the original series were re-operated by the senior author. None of this series' patients underwent carotid angioplasty or stenting.

Discussion

This study has the limitations and biases associated to all retrospective studies. Only 43 patients out of 216 were studied. The clinical evolution of the non-studied patients is not known. However, none of the non-studied 173 patients from the original series were re-operated by the senior author. This study embodies an initial effort for identifying factors and variables that could affect the prognosis of Hispanics that undergo carotid endarterectomy. Using this initial information, prospective and more detailed and comprehensive studies can be designed.

The durability of the carotid endarterectomy is a critical factor in the indication and recommendation of this procedure. Carotid artery restenosis has been reported with an incidence of 1% to 37% (21). Most carotid restenosis cases are asymptomatic and tend to occur in the early postoperative period. Some of the early carotid restenosis cases are thought to be related to technical problems, like residual atheroma plaque after the procedure (19, 21). Other causes of early restenosis include intraluminal thrombi, vessel kinks, vein patch irregularities, accelerated dense scarring, and intimal flaps (23). However, some authors consider that small intimal flaps may not be critical (23). The current series has shown that there was no residual stenosis after an initial CEA as documented by the Duplex scan. Late recurrent stenosis is primarily attributed to myointimal hyperplasia and/or recurrent atherosclerotic plaque (24). Several reported studies have assessed the association between known risk factors for atherosclerosis and the development of carotid restenosis after endarterectomy (25-26). None of these studies have demonstrated a significant correlation between age, sex, hypertension, smoking, hyperlipidemia, diabetes mellitus, and restenosis after CEA (25-26). However, these studies have shown that women have higher recurrent carotid disease, and smokers probably have a higher incidence as well. The observation about a higher incidence of restenosis in women may be attributed to sex-related differences in platelet function and/or a smaller arterial diameter (27-29).

There is a consensus in the literature that endarterectomy or CAS could be considered for symptomatic recurrent stenosis (12, 14). However, the indication of CEA or CAS for restenosis in asymptomatic patients remains without good scientific evidence-based data. Most studies agree that surgery should only be considered if the initial operative risk does not exceed the risk of future stroke (11, 12, 14). In this current series, when asymptomatic recurrent carotid stenosis was detected, sequential noninvasive surveillance of the lesion was done until the stenosis became high-grade (over 70%). There is a controversy as to which represents a better technique, either primary closure or patch repairs (19, 21). In this series of patients with recurrence stenosis the arteriotomy incision was closed with a synthetic patch without further complications during the follow-up period.

There is an ongoing controversy about the role of carotid angioplasty and stenting versus endarterectomy in the treatment of carotid stenosis. Several randomized trials have compared CAE and endovascular treatments (29-35).

The Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS) (30-31) was a large, prospective, randomized, multicenter trial that compared CAE with carotid angioplasty in patients with symptomatic stenosis of at least 70%. Among 504 patients randomized to surgery or angioplasty during 5 years, the rate of any stroke lasting more than 7 days or death within 30 days of first treatment was 10 to 12% in both the surgical and angioplasty groups; and the rate of disabling stroke or death within 30 days of the first treatment was 6% in both groups. Stents were used in only 22% of the patients that underwent angioplasty. The rate of restenosis in the endovascular group was twice that in the surgical cohort (18% vs. 9%, respectively) (30-31).

The Carotid Revascularization Using Endarterectomy or Stenting System (CARESS) (32) trial compared carotid endarterectomy to carotid stenting with protection

devices in patients with carotid stenosis of at least 50% if symptomatic and at least 75% if asymptomatic. The study enrolled 439 patients (254 treated with CAE and 143 with CAS). The 30-day combined all-cause mortality and stroke rate did not differ between surgery (2%) and stenting (2%) (32).

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) (35) trial compared CAE and CAS using an embolic protection device in 334 surgically high-risk patients with more than 50% symptomatic stenosis or more than 80% asymptomatic stenosis. The authors concluded that stenting with distal embolic protection was not inferior to endarterectomy. The results of a 3 year follow-up demonstrated no significant differences between the two groups. More than 20% of the patients in each group had recurrent restenosis following a previous endarterectomy (35).

The SPACE trial conducted in Europe included 1183 patients with symptomatic eye or brain ischemia and more than 50% stenosis (34). The patients were randomized between CAE (599 patients) and CAS (584 patients). The rate of death or ipsilateral ischemic stroke at 30 days was 6.34% with endarterectomy and 6.84% with stenting. Older patients and women tended to do worse with either treatment (34).

The French trial Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis of CAE vs. CAS (EVA-3S) (29) was ended after 527 randomizations. The 30-day rate of stroke and death was higher in the stenting group (9.6%) than in the endarterectomy cohort (3.9%) (p=0.01) (29).

A recent review of the literature concluded that there is no significant difference in the results achieved with CEA and CAS (12). Also, the literature has quoted that high-risk patients for CEA should be given the option to consider CAS as the initial procedure (12, 14). Restenosis after CEA has been classified as a high-risk procedure and, therefore, some authors have mentioned that CAS could be the initial treatment of choice (12). However, patients with heavily calcified plaques, a complex aortic arch, excessively tortuous vessels, or internal carotid arteries with a lumen diameter less than 3 mm are likely better served with endarterectomy (12). These conditions increase the risk of complications during the CAS procedure.

A large, ongoing multicenter trial the Carotid Revascularization Endarterectomy vs. Stent Trial (CREST) sponsored by the National Institute of Neurological Disorders and Stoke is still pending to publish its results (36-37).

Recent publications and the Cochrane review suggest that currently there are no major differences in the results between CAE and CAS (38). Besides the 30-day mortality and morbidity for endarterectomy and stenting, the durability of the procedures can be a determinant factor in selecting which offers better protection against cerebral ischemia on the long-term follow-up. The very long-term durability of these procedures (10 years or longer) has not being compared one against the other.

General racial differences have been reported in stroke epidemiology data (39). Stroke is a leading cause of death in US Hispanics (39). However, little published information is available about the epidemiology of stroke in Hispanics. Vital statistics data indicate similar death rates for Hispanics and non-Hispanic whites under 65 years of age, with lower rates for Hispanics at age 65 and over. Stroke accounted for a somewhat lower percentage of deaths in Hispanics than in non-Hispanic whites; hemorrhagic stroke was slightly more frequent in Hispanics. US Hispanics have higher levels of diabetes, smoking, and overweight, but lower levels of blood pressure and serum cholesterol compared with non-Hispanic whites. No prospective cohort studies have published data on stroke incidence or risk factors in US Hispanics (39). It has been reported that African-Americans have higher stroke prevalence and mortality than whites (1). Aside from that, there is little information about the rate of asymptomatic restenosis after carotid endarterectomy in a Hispanic population. The population studied had a long-term stroke-free rate after carotid endarterectomy, with a low incidence of restenosis. In this particular patient series, with a significant high-grade restenosis (over 70%), carotid endarterectomy was feasible and safe. In conclusion, the incidence of recurrent stenosis of carotid arteries in this study is slightly less, but comparable to other reported studies in non-Hispanic populations with the same risk factors.

Resumen

Uno de los principales procedimientos quirúrgicos para tratar la estenosis y la reestenosis de las arterias carótidas es la endarterectomía. Aunque existe información en la literatura sobre la recurrencia de estenosis posterior a la endarterectomía que demuestra la durabilidad y seguridad de este procedimiento, ésta es limitada en las poblaciones hispanas. Se evaluó de forma retrospectiva la información del expediente médico de todos los pacientes operados de endarterectomía carotídea por el autor principal en los Hospitales de Veteranos de San Juan y el Hospital Pavía. Los expedientes médicos de todos los pacientes que habían sido clínicamente evaluados mediante ultrasonografía Duplex al menos anualmente y por un periodo mínimo de cinco años fueron seleccionados para este estudio. Se identificaron 43 pacientes con estenosis de las carótidas

documentada sometidos a 47 procedimientos (4 pacientes fueron operados bilateralmente). También, se obtuvo información de los factores de riesgo conocidos para el desarrollo de ateroesclerosis, patología principal de la estenosis arterial. En el periodo de seguimiento se identificaron dos pacientes con recurrencia de dicha patología. Los factores de riesgo predominantes para toda la población estudiada fueron hipertensión (58%), hipercolesterolemia (50%), uso de tabaco (46%) y uso de alcohol (36%). Este estudio sugiere que, al igual que en otras poblaciones no hispanas, la endarterectomía es un procedimiento excelente para evitar la isquemia cerebral producida por la estenosis de las arterias carótidas. Además, es confiable y duradero.

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