Background and Purpose—To evaluate the periprocedural outcome after carotid artery stenting with embolic brain protection (EBP+) versus without embolic brain protection (EBP−).

Methods—We retrospectively reviewed data from a prospective nonrandomized database of 357 patients who underwent carotid artery stenting in the neuroradiology division of our institution from 1999 to 2009. One hundred five patients underwent angioplasty and stenting without distal protection, whereas 252 were treated with distal protection. Patients were analyzed according to their EBP status (+ or −) for the primary end points of perioperative stroke, death, or myocardial infarction.

Results—Unprotected stenting was mostly performed in the early years of this study and this is reflected in significant baseline differences between the two groups. In our earlier experience, carotid artery stenting was used in patients with more significant comorbidities. Diabetes mellitus (P=0.04), previous coronary artery disease (P=0.02) and myocardial infarction (P=0.04), and symptomatic lesion (P=0.01) were significantly more common in the EBP− cohort. Despite these baseline differences, there were no significant differences in the primary end points (2% in the EBP+ group and 4.8% in the EBP−, P=0.15). The incidence of ipsilateral stroke in the EBP− and in the EBP+ group was 3.8% versus 0.8%, respectively (P=0.06). There were 2 perioperative deaths (1 in each group) and 4 myocardial infarctions (3 in the EBP+ arm and 1 in the EBP− arm, all non-Q infarcts; P=nonsignificant).

Conclusions—In accordance with recent literature, this series cast doubts as to the real effectiveness of distal embolic protection devices in reducing periprocedural complications. (Stroke. 2011;42:1962-1966.)

Key Words: carotid artery stenting ▪ carotid stenosis ▪ complications ▪ distal protection devices ▪ thromboembolic complications ▪ carotid stenosis

Recent advances in endovascular techniques have added a feasible alternative to conventional surgical repair for the management of carotid diseases. Percutaneous carotid artery stenting (CAS) has the potential of being minimally invasive, less traumatic, and safer in patients with high surgical risk than carotid endarterectomy. The main limitation of CAS is the risk of distal cerebral embolization caused by mobilization and migration of plaque fragments. Although cerebral protection devices have been developed and are widely used to prevent periprocedural cerebral embolization, their application may result in additional complications. There are only 2 very small randomized studies that have evaluated the efficacy of such devices. These studies have suggested that protection devices may not be effective in reducing perioperative distal emboli and arguments have been formulated against their routine use. We reviewed our experience with >350 consecutive CASs and compared the incidence of perioperative complications in patients treated with and without distal protection.

Methods
We performed a retrospective review from a prospective database of consecutive CAS procedures done in the Neuroradiology Suite at the Mayo Clinic, Rochester, MN, from March 1999 to October 2009. Patient evaluation, intervention, and periprocedural evaluation were carried out by a team of neurologists, interventional neuroradiologists, neurosurgeons, and vascular surgeons. Patients with recurrent lesion after previous CAS were excluded. All CAS procedures were divided into 2 groups, protected embolic brain protection (EBP+) and nonprotected (EBP−) arms, on the basis of the use of the distal embolic brain protection device.

Patients were considered symptomatic if they had an ipsilateral amaurosis fugax or transient or persistent focal symptoms felt to be caused by cerebral ischemia. Data were collected regarding various risk factors, including preoperative renal insufficiency defined as a serum creatinine value >1.3 mg/dL; coronary artery disease defined on the basis of an abnormal stress test, previous myocardial infarction on electrocardiography, or a history of coronary artery revascularization (open or percutaneous); chronic obstructive pulmonary disease identified on pulmonary function studies or ongoing need for an inhaler or steroid treatment. Diabetes, hyperlipidemia, hypertension, and congestive heart failure were identified in patients undergoing active medical or dietary treatment.
Table 1. Patients’ Demographics, Risk Factors, and Comorbidities

<table>
<thead>
<tr>
<th></th>
<th>EPD+, No. (%)</th>
<th>EPD−, No. (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>71±9</td>
<td>70±10</td>
<td>0.3</td>
</tr>
<tr>
<td>Male</td>
<td>180 (71)</td>
<td>69 (66)</td>
<td>0.6</td>
</tr>
<tr>
<td>Female</td>
<td>72 (29)</td>
<td>36 (34)</td>
<td>0.4</td>
</tr>
<tr>
<td>Symptomatic stenosis</td>
<td>105 (42)</td>
<td>63 (60)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>220 (87)</td>
<td>90 (85)</td>
<td>0.9</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>204 (81)</td>
<td>82 (78)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>69 (28)</td>
<td>40 (39)</td>
<td>0.04</td>
</tr>
<tr>
<td>Smoker</td>
<td>82 (32)</td>
<td>38 (36)</td>
<td>0.3</td>
</tr>
<tr>
<td>CHF</td>
<td>23 (9)</td>
<td>13 (12)</td>
<td>0.3</td>
</tr>
<tr>
<td>CAD</td>
<td>150 (60)</td>
<td>59 (55)</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous MI</td>
<td>64 (25)</td>
<td>38 (36)</td>
<td>0.04</td>
</tr>
<tr>
<td>COPD</td>
<td>57 (23)</td>
<td>23 (22)</td>
<td>0.9</td>
</tr>
<tr>
<td>CRI</td>
<td>58 (23)</td>
<td>33 (31)</td>
<td>0.1</td>
</tr>
<tr>
<td>PAD</td>
<td>54 (21)</td>
<td>25 (24)</td>
<td>0.7</td>
</tr>
<tr>
<td>Tumors</td>
<td>69 (27)</td>
<td>36 (35)</td>
<td>0.2</td>
</tr>
<tr>
<td>Recurrent stenosis</td>
<td>57 (23)</td>
<td>23 (22)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

EPD+ indicates embolic protection device used; EPD−, embolic protection device not used; CHD, congestive heart failure; CAD, coronary artery disease; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; PAD, peripheral artery disease.

Significant stenosis requiring treatment was considered a stenotic lesion >50% in symptomatic patients or >80% in asymptomatic patients. Patient characteristics are summarized in Table 1.

Primary and Secondary End Points

The primary study end points were periprocedural stroke, myocardial infarction, and death; secondary end points included acute carotid thrombosis, major renal, pulmonary, or cardiac complications, and intensive care unit and hospital length of stay. Stroke was diagnosed on the basis of new neurological deficit. Renal function impairment after stenting was defined as a serum creatinine concentration >1.3 mg/dL in patients with previous normal renal function or an increase >0.2 mg/dL in patients with preprocedural renal insufficiency, measured during the hospital period. Cardiac complications, which included myocardial infarction (MI) and arrhythmias, were defined by clinical symptoms associated with elevation of biochemical markers and electrocardiography findings. Arrhythmia was defined as pulse rate <60 beats/min or >100 beats/min or persistent rhythm alteration on telemetry during the intensive care unit stay. Transient arrhythmias occurring during the procedure were not considered. Pulmonary complications were defined as ventilator dependence for >6 hours after the procedure, need of postoperative intubation, clinical data or culture confirmation of pneumonia, or the need of tracheostomy. Abnormal SpO2 was defined as a value of oxygen saturation <90% measured with pulse oximeter.

Technique

Patients were premedicated with 75 mg clopidogrel per day and 325 mg aspirin per day starting 5 days before the procedure or given a loading dose immediately before the procedure and continued for a minimum of 4 weeks. The procedure was performed under local anesthesia and this permitted careful clinical assessment during each step. However, general anesthesia was preferred in a few cases of uncooperative patients or when difficult and tortuous proximal anatomy made catheterization challenging. Brachiocephalic angiography with intracranial views always preceded stenting. The percentage stenosis was based on the angiographic findings and calculated using North American Symptomatic Carotid Endarterectomy Trial (NASCET) method in all cases.6 When the distal protection tech-

Data Analysis

Statistical analysis was performed using JMP 8.0 (SAS Institute Inc) software. Proportions were compared by using χ2 or Fisher exact tests, as appropriate. Logistic regression models were used to analyze only the association with stroke outcome variables (the rates of death, MI, and restenosis were too low to allow any valid analysis of predictors of these outcomes). Univariate logistic regression models were fit for each variable. Results are reported with OR, 95% CI for PR, and probability value. Multivariate analysis was not pursued for any of the end points because of low event rates. P<0.05 was considered significant for all analyses.

Results

Patient Characteristics

Three hundred fifty-seven CASs were included in this study. Symptomatic lesions were significantly more common in the EBP− group (60% versus 42%, P=0.01) as well as a history of diabetes mellitus (P=0.04) and previous MI (P=0.04), reflecting use of CAS only in very high-risk populations in the early part of the experience. Demographic and clinical data are summarized in Table 1.

Intraoperative Data

Distal balloon occlusion was used for distal protection in 24 cases, whereas in 228 cases, distal filters were used. The angiographic characteristics of the patients included in this series are summarized in Table 2. In each group, patients were divided into 4 subsets according to the timing of percutaneous transluminal angioplasty. In the EBP− arm, postdilatation alone and primary stenting were performed significantly more frequent than in the EBP+ arm (P=0.01 and P<0.001, respectively) reflecting different operators’ preference. The prestenting dilatation and pre- and poststenting dilatations were used with similar frequency in the 2 groups. The percentage of residual stenosis after the procedure (divided into 3 levels, 1 <20%; 2=20% to 40%; 3 >40%) was not different between the 2 groups.

Morbidity and Mortality

Periprocedural ipsilateral stroke, MI, and mortality are presented in Tables 3 and 4. The overall stroke rate was 1.7% (patients with symptomatic carotid stenosis, 2.4%; patients with asymptomatic carotid stenosis, 1.1%). Two of the 6 strokes were related to acute in-stent thrombosis, and the others were considered to be the result of embolism. Among
patients who experienced embolic stroke, 3 were treated with pre- (before stenting) dilatation alone (1 in protected CAS and 2 in nonprotected CAS) and 1 underwent postdilatation alone (nonprotected group) and the difference was not significant (P=0.09).

Stroke rate was higher in patients with symptomatic carotid disease in both groups (EBP+: symptomatic, 1.0%; asymptomatic, 0.7%; EBP−: symptomatic, 4.75%; asymptomatic, 2.4%), but these differences were again not statistically significant.

Overall mortality was 0.6% (symptomatic, 0.6%; asymptomatic, 0.5%). The difference in mortality between the EBP+ group (0.4%) and EBP− group (0.95%) was not significant. The low event rate (n=2) did not allow further statistical analysis of predictors of postoperative death. Four myocardial events were observed (all non-Q wave). Three (1.2%) occurred in the EBP+ and 1 (1.0%) in the EBP− group (P=nonsignificant).

When only patients treated with distal filter devices were considered (n=228), the stroke rate was 0.8% versus 3.8% in the nonprotected CAS group (P=0.08). There were 3 MIs (1 less than in all protected CASs) and the overall stroke/death/MI was 1.7% (2% in all protected CASs). When compared with the nonprotected (EPD−) group, the primary combined end point of stroke/death/MI was not statistically significant (P=0.15). Temporary or permanent increases of serum creatinine concentration were seen in 6 patients in the EBP+ arm and in 9 patients in the EBP− arm (P=nonsignificant). The incidence of restenosis after the procedure was mildly higher in the EBP+ than in the EBP− (P=0.054). Hospital length of stay was 2.1±2.5 days and 2.3±2.6 days (P=nonsignificant) in protected and unprotected arms, respectively. Finally, intensive care unit stay was longer in the unprotected group than in the EBP+ group (Table 5). Other minor adverse events included groin hematoma (EBP+: 2% versus EBP−: 2.9%; P=nonsignificant), confusion after procedure (EBP+: 1.6% versus EBP−: 6%; P=0.027), arrhythmia (EBP+: 3.7% versus EBP−: 6.1%; P=nonsignificant), and abnormal SpO2 (EBP+: 29.6% versus EBP−: 48.6%; P=0.003).

**Clinical Predictors**

Age ≥70 years was significantly associated with 2.1-fold increase in stroke when considering all cases combined. We found no other variable to be associated with the risk of stroke.

**Discussion**

Distal protection devices have become “standard of care” during angioplasty and stenting for carotid artery stenosis. These devices “… appear seductively simple, elegant, and beneficial to both physician and patients,” yet there is no strong evidence that distal protection is effective in reducing the incidence of thromboembolic complications during CAS.6,11–17 We found no significant differences in the incidence of thromboembolic complications during CAS.6,11–17 We found no significant differences in the incidence of thromboembolic complications during CAS.
dence of perioperative stroke, MI, and death rates between patients treated with or without distal protection. There was a slightly higher incidence of perioperative strokes in the nonprotected group, which did not reach statistical significance. The EBP− group reflected mostly our early experience (including the very first cases) with devices not specifically designed for use in the carotid system and less operator experience (1999 to 2003; Figure). Moreover, symptomatic status (a known risk factor for periprocedural ischemic complications) was significantly more common in the EBP− group (60% versus 42%, P<0.01).

During CAS, there is a real risk of dislodging microemboli after each stage of the procedure (crossing the lesion, prestent angioplasty, stenting, and poststent angioplasty). Protection devices have been designed in an attempt to reduce the risk of distal microemboli. The concept is theoretically very appealing, but in practice, there are several factors limiting the true efficacy of distal protection. The first is the need to cross the lesion before protection is achieved. The second drawback is related to the stiffness of these devices, which makes navigation through the stenosis challenging, especially in the presence of proximal and/or distal (to the stenosis) tortuosity (very common in patients with atherosclerotic disease). The filter “recatch” phase is another potential generator of distal emboli. Despite adequate restoration of carotid lumen after CAS, it is possible that the “bulky” protection device may dislodge plaque debris protruding through the stent struts during the retrieval phase.

In the absence of Class I evidence, indirect observational studies—often with historical controls—initially supported the use and suggested potential efficacy of distal protection during CAS. However, more recent and stronger data have questioned the effectiveness of distal protection. A subanalysis of pooled data from multicenter trials of CAS for symptomatic stenosis (Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis [EVA-3S], Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy [SPACE]) failed to show a clear benefit of “protected” versus unprotected CAS in reducing periprocedural ipsilateral ischemic events. Similarly, in the recent International Carotid Stenting Study (ICSS), the rate of stroke in the group treated with protection devices was higher (5.1%) than in the group in which no protection was used (2.4%). In this same study, the rate of MRI diffusion-weighted abnormalities after CAS was also higher in the protected group. Finally, Tietke et al retrospectively analyzed 358 unprotected CAS, reporting a very low (2%) rate of periprocedural stroke suggesting that “safe” CAS can be performed without such adjuncts. Our observation is in line with the conclusions of these studies questioning the efficacy of these devices.

To avoid some of the problems encountered with “filter-type” protection devices, other concepts have been proposed to reduce the incidence of distal emboli. Flow reversal can be achieved with a triple lumen-guiding balloon catheter with an additional distal occlusion balloon. Flow is arrested through the common carotid artery by inflating the balloon catheter and reversed by occluding the external carotid with the distal balloon. The reversed flow is directed through the guiding catheter, which is externally connected to a blood-filtered femoral vein line. Although appealing, superiority of flow-reversal devices over “filter types” has not been tested in a randomized study.

Among patients with asymptomatic carotid stenosis, the risk of stroke or death was 1.3% with EBP and 2.4% without EBP, which could be higher than with modern intensive medical therapy alone. However, our asymptomatic patients undergoing the intervention were a selected population and these often had progression of plaques despite aggressive medical treatment. Whether stenting or endarterectomy can be justified for patients with asymptomatic stenosis is currently a matter of debate. Future studies of endarterectomy or stenting in asymptomatic stenosis should have a medical arm.

Our study has several limitations. Nonprotected stenting was mainly performed in the first phase of the institutional experience with operators having different backgrounds, techniques, and levels of experience. However, in theory, these differences should have been an advantage for the protected group because distal protection was used almost
routinely in the most recent part of the experience when operators had already acquired greater expertise in CAS and patients undergoing CAS were not as complicated (in terms of significant comorbidities) as was commonly the case in the early years of CAS. Moreover, this is the largest single-center study comparing protected and unprotected CAS to our knowledge with precise criteria of data collection and independent vascular neurologist assessment of most patients, resulting in high-quality and a large spectrum of information for each patient.

Conclusions

In line with recent experience, our observation questions the real efficacy of routine distal protection during CAS. It is likely that improved technology and the design of refined distal protection devices in the near future may overcome some of the current limitations. Given the large number of CAS procedures already being performed in North America and the likely increase in the use of this revascularization technique after the publication of the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) results, these observations call for a well-designed multicenter study to determine the value of distal protection in CAS.

Disclosures

None.

References

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경동맥 혈관성형술과 스텰트술에서 원위보호기구의 ‘보호적’ 효과가 있는가?

Are Distal Protection Devices ‘Protective’ During Carotid Angioplasty and Stenting?

Tiziano Tallarita, MD; Alejandro A. Rabinstein, MD; Harry Cloft, PhD; David Kallmes, MD; Gustavo S. Oderich, MD; Robert D. Brown, MD; Giuseppe Lanzino, MD


Key Words: carotid artery stenting ■ carotid stenosis ■ complications ■ distal protection devices ■ thromboembolic complications ■ carotid stenosis

배경과 목적
본 연구에서는 뇌섬전보호기구(embolic brain protection)의 사용 여부에 따른 경동맥 스텰트술(carotid artery stenting) 후 시술 주변 합병증의 차이를 평가하고자 하였다.

방법
연구자들은 1999년부터 2009년까지 본 기관의 신경영상과에서 경동맥 스텰트술을 받은 357명의 전향적 비무작위 데이터 베이스 자료를 후향적으로 조사하였다. 105명의 환자들이 원위보호기구 없이 시술을 받았고, 252명은 원위보호기구를 사용하여 시술을 받았다. 뇌섬전보호기구 사용 여부에 따른 스텰트술 전후 뇌졸중, 사망, 또는 심근경색을 포함한 일차 종말점 의 차이를 분석하였다.

결과
연구 기간 중 초기에는 대부분 보호기구 없이 스텰트술을 시행하였고, 이로 인하여 양측 군에 기저 특성의 유의한 차이가 있었다. 초기 경동맥 스텰트슬은 더 위중한 동반 질환을 가진 환자들에서 주로 시행되었다. 뇌섬전보호기구를 사용하지 않은 군에서 당뇨병(P=0.04), 관상동맥질환(P=0.02)과 심근경색의 확률(P=0.04), 증상성 병변(P=0.01)이 더 혼합하였다. 이러한 기저 특성의 차이에도 불구하고, 두 군 간의 일차 종말점의 차이는 유의하지 않았다(뇌섬전보호기구 사용군: 2%, 미사용군: 4.8%, P=0.15). 뇌섬전보호기구 미사용군과 사망군에서 동측 뇌졸중 발생은 각각 3.8%와 0.8%였다(P=0.6), 2명의 시술 주변 사망(각 군 1명)과 4명의 심근경색(뇌섬전보호기구 사용군: 3명, 미사용군: 1명, 모두 비Q 경색)이 발생하였다(P=non-significant).

결론
최근의 문헌 보고와 마찬가지로 이 연구 결과도 원위보호기구가 시술 주변 합병증 감소에 정량 효과가 있는지 의구심을 가지게 한다.
Table 3. Major Adverse Events After Carotid Artery Stenting for Patients Who Underwent Protected CAS Compared With Nonprotected CAS

<table>
<thead>
<tr>
<th>Event</th>
<th>EPD+ (N=252; %)</th>
<th>EPD− (N=105; %)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/death/MI</td>
<td>5 (2)</td>
<td>5 (4.8)</td>
<td>0.2*</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.4)</td>
<td>1 (0.95)</td>
<td>0.5*</td>
</tr>
<tr>
<td>Ipsilateral stroke</td>
<td>2 (0.8)</td>
<td>4 (3.8)</td>
<td>0.06*</td>
</tr>
<tr>
<td>MI</td>
<td>3 (1.2)</td>
<td>1 (0.95)</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

EPD+ indicates embolic protection device used; EPD−, embolic protection device not used; MI, myocardial infarction.

*Fisher exact test used.

Table 4. Major Outcomes in Symptomatic and Asymptomatic Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Asymptomatic No. (%)</th>
<th>Symptomatic No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EPD+ (n=147)</td>
<td>EPD− (n=42)</td>
</tr>
<tr>
<td>Stroke/death/MI</td>
<td>3 (2.1)</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (0.7)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>MI</td>
<td>2 (1.4)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

EPD+ indicates embolic protection device used; EPD−, embolic protection device not used; MI, myocardial infarction.

*Fisher exact test.

Figure. Distribution of carotid artery stenting (CAS) according to the use of an embolic brain protection device.