Introduction

The Gateway balloon-Wingspan stent system (Boston Scientific, Fremont, CA), a stenting system specifically designed for the cerebrovasculature, became commercially available in the United States in 2005. The US Wingspan Registry is a 5-center collaboration in which data were prospectively collected from 158 consecutively treated patients with symptomatic intracranial atherostenosis.1 Patient and Institutional Enrollment

Patients and Methods

The Gateway-Wingspan system was prospectively attempted treatment with the Wingspan system were prospectively

Background and Purpose—The purpose of this study is to present 12-month follow-up results for a series of patients undergoing percutaneous transluminal angioplasty and stenting with the Gateway-Wingspan stenting system (Boston Scientific) for the treatment of symptomatic intracranial atherostenosis.

Methods—Clinical and angiographic follow-up results were recorded for patients from 5 participating institutions. Primary end points were stroke or death within 30 days of the stenting procedure or ipsilateral stroke after 30 days.

Results—During a 21-month study period, 158 patients with 168 intracranial atherostenotic lesions (50% to 99%) were treated with the Gateway-Wingspan system. The average follow-up duration was 14.2 months with 143 patients having at least 3 months of clinical follow-up and 110 having at least 12 months. The cumulative rate of the primary end point was 15.7% for all patients and 13.9% for patients with high-grade (70% to 99%) stenosis. Of 13 ipsilateral strokes occurring after 30 days, 3 resulted in death. Of these strokes, 76.9% (10 of 13) occurred within the first 6 months of the stenting procedure and no events were recorded after 12 months. An additional 9 patients experienced ipsilateral transient ischemic attack after 30 days. Most postprocedural events (86%) could be attributed to interruption of antiplatelet medications (n=6), in-stent restenosis (n=12), or both (n=1). In 3 patients, the events were of uncertain etiology.

Conclusions—After successful Wingspan percutaneous transluminal angioplasty and stenting, some patients continued to experience ipsilateral ischemic events. Most of these ischemic events occurred within 6 months of the procedure and were associated with the interruption of antiplatelet therapy or in-stent restenosis. (Stroke. 2011;42:1976-1981.)

Key Words: angioplasty ■ intracranial atheromatous disease ■ stenting ■ symptomatic intracranial stenosis ■ Wingspan
enrolled into a multicenter intention-to-treat registry (US Wingspan Registry) that included the Barrow Neurological Institute, Cleveland Clinic, State University of New York at Buffalo, University of Texas Southwestern, and University of Wisconsin. The Institutional Review Board at each institution approved the use of the Wingspan system under a Humanitarian Device Exemption as well as the collection and sharing of registry data among the participating centers.

Data Collection
Clinical and angiographic data were typically collected at the time of the initial procedure and at 3 to 6 months and 12 to 15 months. Clinical data were also collected at discharge and between 2 and 6 weeks after the original procedure.

Stenting Technique
Percutaneous transluminal angioplasty and stenting (PTAS) was performed using the Wingspan system as described previously. In brief, access was typically achieved through the common femoral artery. Most cases were performed through a 6-Fr guiding catheter or long sheath system. Heparinization was instituted to a targeted activated coagulation time of 250 to 300 seconds. In most cases, after conventional catheter-based angiography, an SL-10 (Boston Scientific, Natick, MA), Prowler-10 (Cordis), or Echelon-10 (Microtherapeutics, Irvine, CA) microcatheter was manipulated across the target lesion using a 0.014-inch Synchro (Boston Scientific) or Transcend EX Soft Tip (Boston Scientific) microwire. The microcatheter was then exchanged over a 0.014-inch exchange microwire for a Gateway angioplasty balloon. The remaining lesions were primarily crossed with the Gateway angioplasty balloon and 0.014-inch exchange-length microwire. In each case, the balloon diameter was sized to 80% of the “normal” parent vessel diameter. The balloon length was selected to match the lesion length. Angioplasty was typically performed with a slow, graded inflation of the balloon to a pressure of between 6 and 12 atmospheres for approximately 120 seconds. After angioplasty, the balloon was removed and conventional angiography was repeated.

Next, the Wingspan delivery system was prepared and advanced over the exchange wire across the target lesion. The stent diameter was sized to exceed the diameter of the normal parent vessel by 0.5 to 1.0 mm. The stent length was selected to equal or exceed the length of the angioplasty balloon and to completely cover the entire diseased segment. The diameter of the stenotic lesion was measured using biplane angiography and compared with a reference diameter of the normal vessel (usually proximal to the lesion) per the technique used in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study.

All patients were pretreated with antiplatelet agents (aspirin and clopidogrel); most were discharged on both aspirin (325 mg daily) and clopidogrel (75 mg daily). The dual antiplatelet regimen was usually maintained until follow-up angiography was performed. Provided that no ISR had developed, clopidogrel was usually discontinued after follow-up angiography. All patients remained on aspirin therapy (325 mg daily) indefinitely after treatment.

Follow-Up Imaging
Imaging follow-up was available for 138 lesions. Most of the lesions (n=109) were evaluated with conventional catheter-based angiography. In some cases, lesions were evaluated with CT angiography (n=28). If the entire stented segment as well as the proximal and distal parent vessel was well visualized and widely patent on CT angiography, these stents were designated as demonstrating “no ISR.” If a region of the stented segment or adjacent parent vessel could not be adequately visualized, catheter angiography was performed. In cases in which the findings on the cross-sectional imaging were ambiguous or suggestive of ISR, conventional angiography was performed. In 1 case, only MR angiography was available as a follow-up examination.

At angiographic follow-up, the minimum luminal diameter was identified and measured. The percentage of residual or recurrent stenosis was calculated using the WASID technique. ISR was defined as a lesion demonstrating (1) >50% stenosis (ie, within or immediately adjacent [within 5 mm] to the stent); and (2) >20% of absolute luminal loss. The measurements were made by the authors at each institution and then adjudicated by 1 investigator (D.J.F.). Lesion retreatment was performed at the discretion of the primary operator.

Clinical Event Adjudication
Scheduled clinical follow-up occurred at the time of discharge and at 2 to 6 weeks, 3 to 6 months, and 12 to 15 months after the Wingspan procedure. Any stroke or death occurring during or within 30 days of the procedure or any stroke within the ipsilateral vascular distribution after 30 days was counted as a primary neurological end point. For the purpose of the present analysis, any hemorrhagic or ischemic event resulting in a new neurological deficit lasting >24 hours was considered a stroke. Any ischemic event resulting in a transient neurological deficit that resolved within 24 hours was considered a transient ischemic attack (TIA) regardless of the neuroimaging findings. The distribution of the stroke (ipsilateral or other) was adjudicated on the basis of the neurological findings evaluated within the context of any available neuroimaging study. End point adjudication was determined by investigators at the individual sites.

Results

Registry Patients
During a 21-month study period, 158 patients with 168 intracranial atherostenotic lesions (50% to 99% severity) were treated with the Gateway-Wingspan system. Patients (95 men, 63 women) ranged in age from 33 to 86 years (average age, 62.7 years). Ninety patients presented with a qualifying event of stroke (57%). The average stenosis treated measured 75.2%, and 115 of the treated lesions (69%) were in the 70% to 99% stenosis range at presentation. Periprocedural stroke was encountered in 9 patients (5.7%). In 4 patients (2.5%), these strokes ultimately resulted in death.

Clinical Follow-Up
Of the initial group of 158 patients, 147 were eligible for 3-month follow-up evaluation allowing for loss to periprocedural primary end points (n=9) or nonneurological death occurring after 30 days (n=2). A total of 143 of these patients (97.3%) had at least 3 months of clinical follow-up. One hundred ten of 127 eligible patients (86.6%) had at least 12 months of follow-up. The average length of clinical follow-up for the registry patients was 14.2 months.

The cumulative rate of the primary end point was 15.7% for all patients and 13.9% for patients with high-grade (70% to 99%) stenosis. Of 13 ipsilateral strokes occurring after 30 days, 3 resulted in death. Ten of 13 (76.9%) of the ipsilateral strokes that occurred after the 30-day periprocedural period occurred within 6 months of the procedure, and no events were recorded after 12 months. An additional 9 patients experienced an ipsilateral TIA after 30 days. The composite rate of either stroke or TIA between 30 days and 12 months was 20% (22 total events in 110 patients with 12-month clinical follow-up).

Most postprocedural events (86%) were associated with interruption of antiplatelet medications (n=6), ISR (n=12),
or both (1). In 3 patients, the events were of uncertain etiology. Specifically, for the 13 patients meeting the primary end point with ipsilateral ischemic stroke after 30 days, 5 were believed to be due to ISR and 5 to the interruption of antiplatelet medication; and in 3, a specific cause was not determined. Patients experiencing stroke from interruption of antiplatelet medications presented between 2 and 9.5 months (average, 4.4 months) postprocedure (Figure 1 through 3). Patients experiencing stroke as a result of ISR presented between 3.5 and 11.5 months (average, 6.9 months) postprocedure (Figure 4). Two patients who experienced stroke at 10.5 and 11.5 months, respectively, skewed the average time of presentation for stroke associated with ISR. These patients had been transiently symptomatic with ISR at earlier time points and had undergone ≥1 repeat angioplasties before ultimately presenting with stroke from recurrent ISR. The average time of presentation for patients with an unknown cause of stroke was 3.2 months (range, 1.5 to 5 months). In the 9 patients experiencing an ipsilateral TIA after 30 days, 7 events were associated with ISR, 1 to the interruption of antiplatelet medication; and in 1 patient, both factors were present.

Discussion

The most important findings derived from the present analysis of the US Wingspan Registry are (1) some patients continue to experience ipsilateral ischemic events after initially successful PTAS with the Gateway-Wingspan system; (2) most of these delayed events can be attributed to defined factors, either early interruption of antiplatelet medication or ISR; and (3) these delayed ischemic events most frequently occurred within the first 6 months after treatment.

The Gateway-Wingspan system was introduced in 2005 as a novel strategy for the treatment of symptomatic intracranial atherosclerosis. The initial experience with the system indicated that the angioplasty and stenting procedure could be achieved with rates of periprocedural stroke (approximately 5%) that compared very favorably with event rates in selected high-risk patients treated medically.1,3–5 However, midterm angiographic follow-up results from 2 independently conducted single-arm registries revealed rates of ISR or complete stent occlusion that ranged between 25 and 35%.2,6–8 These rates of late luminal loss were considerably higher than those reported in the initial Eurasian Humanitarian Device Exemption study.7 Although the majority of patients with ISR were asymptomatic, approximately one third presented with ipsilateral ischemic symptoms.2,6,8 These findings provoked questions about the durability of the treatment modality and the potential for ongoing ischemic events after initially successful treatment. The goal of the present analysis was to address this issue.

Event Rates After the Periprocedural Period

In the present study, some patients continued to accrue ipsilateral ischemic events after initially successful PTAS. These delayed events accounted for almost two thirds of the total number of cumulative events, exceeding those incurred during the actual PTAS procedure. The National Institutes of Health Wingspan Registry reported a 5% to 6% rate of delayed ipsilateral stroke after the periprocedural period in patients with high-grade (70% to 99%) symptomatic stenosis.5 However, although this study provides an excellent assessment of the periprocedural risk of the procedure in >100 patients, 12-month follow-up results were available for very few patients (n=15). As such, these data are probably not sufficient to allow an accurate estimation of postprocedural event rates.5 In the present study, there was no difference observed in either the periprocedural or postprocedural

Figure 1. Adult patient originally presenting with minor stroke at the time of being on aspirin therapy. Subtracted angiogram (A) in the working angle for treatment demonstrates a high-grade (>90%) focal stenosis (dotted circle) of the distal M1 segment of the middle cerebral artery. Subtracted (B) and native (C) images from the control angiogram in the working angle immediately after angioplasty and stenting with the Gateway-Wingspan system (Boston Scientific) demonstrates no significant residual stenosis.

Figure 2. The patient (same patient as in Figure 1) stopped taking antiplatelet medications 6 weeks after the procedure and represented at 8 weeks with new right upper extremity weakness. Axial diffusion sequences (A–C) demonstrate multiple small infarcts within the posterior left frontal lobe (arrows) involving the motor cortex.
event rates between the overall group (50% to 99% stenosis) and those patients presenting with high-grade (70% to 99%) stenosis.

Thus, although the periprocedural stroke risk associated with the PTAS procedure itself (approximately 5%) appears far lower than the risk associated with high-grade (70% to 99%) symptomatic stenosis treated medically (20% to 25% over the first year), the ischemic events occurring beyond the periprocedural period in patients undergoing stenting make the risk profile of the 2 treatment strategies appear far more comparable. As such, a direct comparison between the stenting procedure and medical therapy, as is currently underway in the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial, will be necessary to definitively determine whether stenting can provide a meaningful additional benefit to medical therapy in high-risk patients.

**Etiology of Delayed Events**

In addition to better defining the overall risks related to Wingspan PTAS, it is critical to make an attempt to ascertain the circumstances under which the Wingspan stenting procedure might fail beyond the periprocedural period. In the present study, 2 predictable factors seemed to be associated with the majority (86%) of delayed ischemic events, the interruption of antiplatelet therapy and the development of ISR.

Approximately 40% of delayed strokes were associated with the interruption of antiplatelet medications. Early discontinuation of antiplatelet medications typically results from patient nonadherence, discontinuation in response to hemorrhage or a perceived risk of hemorrhage, in preparation for an upcoming invasive/surgical procedure, or at the discretion of the patient’s primary physician. Conceivably, these events could be largely overcome by more aggressive and proactive education of patients, their families, and all their managing physicians. Dual antiplatelet therapy was typically continued during the present study for 3 to 6 months with discontinuation of clopidogrel contingent on angiographic follow-up confirming the absence of ISR. Thus, intensive clinical follow-up and assurance of adherence to the recommended antiplatelet regimen is most critical during this initial 90- to 180-day period. In the present series, only 1 delayed ipsilateral stroke could be attributed to the interruption of antiplatelet medications after 6 months and this patient had stopped taking all antiplatelet medications.

ISR represents a potential limitation of any stenting procedure. In the present series, ISR was associated with almost 40% of postprocedural stroke events. In addition, the majority of patients within the registry underwent scheduled imaging surveillance of their stents as part of routine clinical follow-up. When identified at follow-up, ISR was typically managed with the continuation of dual antiplatelet therapy. When patients experienced new neurological symptoms or late luminal loss to the extent that the recurrent stenosis was of a severity greater than or equivalent to the presenting lesion before treatment, repeat angioplasty was typically performed. As such, the reported recurrent stroke risk attributable to ISR was observed in the setting of a fairly proactive program of imaging surveillance, medical management, and interventional retreatment. Thus, it seems that measures to reduce the delayed morbidity associated with ISR may be limited to

**Figure 3.** Subtracted image from an angiogram performed at 8 weeks demonstrates no significant in-stent restenosis (same patient as in Figure 1).

**Figure 4.** Adult patient with symptomatic right hemisphere transient ischemic attacks on aspirin therapy. Subtracted image (A) in the lateral projection demonstrates moderate stenosis (arrow) of the supraclinoid segment of the internal carotid artery. Subtracted image (B) in the lateral projection after angioplasty and stenting with the Wingspan demonstrates no significant residual stenosis. Subtracted image (C) in the frontal projection after angioplasty and stenting demonstrates a normal luminal diameter of the supraclinoid internal carotid artery and the M1 segment of the middle cerebral artery. The patient presented with a minor right hemisphere stroke more than 3 months after the procedure while on antiplatelet medications. Angiography demonstrates a high-grade restenosis (D, arrow) at the distal aspect of the Wingspan stent.
strategies designed to improve the existing devices such as the development of drug-eluting balloons, a drug-eluting version of the current self-expanding stent platform, or an optimization of the degree of chronic outward force exerted by the device on the vessel wall.\textsuperscript{12,13}

**Timing of Delayed Events**

The vast majority (80\%) of delayed ischemic symptoms (both TIAs and strokes) occurred within 6 months of treatment. The timing of these events correlates well with the “risk period” of the 2 major factors responsible for recurrent ischemia. The discontinuation of antiplatelet medications is likely to become less of a risk with time as the implanted stent becomes fully “endothelialized” and incorporated into the parent artery. Similarly, the risk associated with ISR is almost exclusively incurred during the first 3 to 6 months after the stenting procedure. Those patients who experienced stroke attributable to ISR at later time points had been symptomatic earlier with TIAs and then represented with stroke after developing recurrent ISR months after angioplasty. The available literature suggests that after this initial 3- to 6-month postprocedural period, the tissue ingrowth along the stented segment stabilizes and, in some cases, actually undergoes a process of reorganization to become somewhat more compact, resulting in partial regression of the angiographic stenosis. This process of stabilization and/or spontaneous regression of ISR has been documented for both coronary and intracranial stents.\textsuperscript{14,15} The present data suggest that if patients with ISR do not become symptomatic during this initial 3- to 6-month period after the procedure and an appropriate medication regimen is maintained, it is unlikely that they will ultimately become symptomatic in follow-up.

**Limitations**

Although the present report represents the longest follow-up of a large series of patients with intracranial atherosclerosis treated with the Wingspan-Gateway system, it is important to acknowledge that the present data set has some significant limitations. Most importantly, not all eligible patients were available for follow-up at the 12-month time period (13\% were lost to follow-up by 1 year). Because there is no guarantee that the patients who were lost to follow-up had event rates that were similar to those who were followed to (and beyond) 12 months, it is important to acknowledge that this represents a potential source of bias with respect to the reported 1-year event rates.

**Conclusions**

After successful PTAS, some patients may continue to experience ipsilateral ischemic events. Most of these events occur within 6 months of the procedure. These ischemic events can largely be attributed to premature interruption of antiplatelet medications or ISR.

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**References**


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미국 Wingspan 등록부
12개월 추적 관찰 결과

US Wingspan Registry
12-Month Follow-Up Results

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Key Words: angioplasty ■ intracranial atheromatous disease ■ stenting ■ symptomatic intracranial stenosis ■ Wingspan

배경과 목적: 본 연구의 목적은 중상성 두개내 축상경화증(intracranial atherostenosis)의 치료를 위하여 페부경유혈관경화 완성형술(percutaneous transluminal angioplasty) 및 Gateway-Wingspan 스테트슬(Boston Scientific)을 받은 환자들 을 12개월간 추적 관찰한 결과를 보고하는 것이다.

방법: 참여 병원 5개소에서 환자들의 임상 및 혈관조영술(angiography) 결과를 기록하였다. 임상 결과 변수는 스테트슬 30일 이내의 뇌출혈 혹은 사망 발생 및 30일 이후 동측의 뇌출혈 발생이었다.

결과: 21개월의 연구 기간 동안, 158명의 환자에서 168개의 두개내 축상경화증 병변(50~99%)에 대하여 Gateway-Wingspan 스테트슬이 시행되었다. 최소 3개월 이상의 임상적 추적 관찰이 완료된 환자 143명에서 평균 14.2개월간 추적 관찰하였으며, 110명에서 12개월 이상의 추적 관찰이 이루어졌다. 임상 결과 변수의 누적 발생률은 모든 환자에서 15.7%였으며, 현저한 혈착 (stenosis)(70~99%)가 있던 환자에서 13.9%였다. 스테트슬 30일 이후에 발생한 동측 뇌출혈 13례 중 3례의 환자가 사망하였다.

이 동측 뇌출혈 가운데 76.9% (13례 중 10례)가 스테트슬 후 6개월 이내에 발생하였으며, 12개월 이후에는 뇌출혈이 발생하지 않았다. 시술 이후에 발생한 사망의 대부분(86%)은 혈활성판재 투약 중단(n=6), 스테트내 재협착(in-stent restenosis)(n=12), 혹은 두 가지 모두(n=1)에 기인하였다. 3례에서는 그 원인이 불명확하였다.

결론: 페부경유혈관경화완성형술 및 스테트슬이 성공한 이후에도 일부 환자에서는 동측의 허혈성 사망이 발생할 수 있다. 이러 한 허혈성 사망의 대부분은 시술 후 6개월 이내에 발생하며, 혈활성판재의 투약 중단 혹은 스테트내 재협착과 연관되어 있다.

경관질환(cerebrovasculature) 치료를 위하여 개발된 Gateway 공간-Wingspan 스테트시스템(Boston Scientific, Fremont, CA)은 미국에서 2005년도에 상업적 판매가 허가되었다. US Wingspan Registry는 5개 병원의 협력 을 통하여 중상성 두개내 축상경화증(intracranial atherostenosis)에서 이 스테트슬을 시행한 환자 158명을 전향적으
로 수록하고 있다. 1 Gateway 풍성형술(balloo angioplasty)을 시행하고 Wingspan 스텀트를 목표한 병변에 걸쳐 설치한 경우, 부부적으로 협착(stenosis)이 나타나지나 시술과 관련된 합병증도 있었다고 하더라도 시술 성공으로 간주하였으며, 각인 결과 6주와는 스텀트가 시험 30일 이상에 발생한 되춤 후 역시 약자가, 그리고 스텀트가 30일 이후에 발생한 독촉의 되춤증으로 정의하였다. 일부 환자에서 시행된 이전의 연구 결과, 본 치료 방법의 시술 전 후 성공은 약물 투여만으로 치료한 대의 편인 경우에 비해 양호한 것으로 확인되었으나, 상당한 숫자에서 스텀트 재협착(in-stent restenosis, ISR) 및 펌러 결함이 혈관조영술(angiography) 추적 검사에서 발생되었다. 2 이러한 결과는 본 시술의 내구성(durability) 및 성공적으로 시술받은 환자에서 동측의 허혈성 사건 발생 위험도에 대한 의구심을 증폭시켰다.

본 연구에서, 저자는 Gateary-Wingspan 스텀트로 치료받은 환자들의 장기 예후를 보고하고자 한다. 일차 결과 변수가 발생한 환자의 임상 자료를 분석하여, 치료 실패의 잠재적인 원인을 밝히고자 하였다.

환자와 방법
환자 및 참여 기관 등록
중앙성 두개내 축성정화중으로 Wingspan 스텀트술을 받은 예정인 환자는 다기관 동록부에 전향적으로 동록되었다(US Wingspan Registry). 본 동록부는 최초 치료 방향 결정에 의거하여 환자를 동록하였으며(intention-to-treat), Cleveland Clinic, State University of New York at Buffalo, University of Texas Southwestern 및 University of Wisconsin에 참여하였다. 각 참여 병원들은 Wingspan 스텀트에 대한 의료 기기 사용의 인도적인 허가 덴체(Humanitarian Device Exemption) 및 참여 기관의 동록부 구성과 자료 공유를 조건으로 은린 위 원회 승인을 취득하였다.

자료 수집
임상 및 혈관조영술 자료는 일반적으로 최초 시술 시점, 3~6개월 및 12~15개월 시점에서 수집되었다. 임상 자료는 퇴원 시점 및 최초 시술 2~6주 후에 추가로 수집하였다.

스텐트술
Wingspan 스텀트를 이용한 피부경유혈관경유혈관조영술 및 스텀트술(percutaneous transluminal angioplasty and stenting, PTAS)은 이전에 기술된 바와 같이 시행되었다. 1 간 락하기, 주로 총대퇴동맥(common femoral artery)을 통하 여 혈관 내로 접근하였다. 대부분의 사례에서 6~8Fr 유도 카테터(guiding catheter) 혹은 long sheath system을 이용하였 다. 혈관으로의 투어하여 활성 응고 시간(activated coagulation time)을 250~300초로 유지하였다. 대부분의 사례에서 카테터를 이용한 혈관조영술을 시행한 후, 0.014인지 Synchro
(Boston Scientific) 혹은 Transand EX Soft Tip (Boston Scientific) 미세와이어(microwire)를 거쳐 SL–10 (Boston Scientific, Natick, MA), Frowler–10 (Cordis) 혹은 Echelon–10 (Microtherapeutics, Irvine, CA) 미세카테터(microcather)를 삽입하여 혈관 협착 부위로 접근하였다. 이후 미세와이어를 거치시킨 상태에서 미세카테터를 Gateway 혈관 성형 풍성형(balloo angioplasty)으로 교체하였다. 잔여 병변은 주로 Gateway 혈관성형 풍성 및 0.014인지 미세와이어를 통해 통과하였다. 개별 사례에서 풍성의 자료는 정상적인 혈관 길이 30%가 되는 것을 선택하였다. 풍성의 길이를 고려하여 적절한 것을 선택하였다. 혈관조영술은 풍성 센서 처서 제단식으로 부풀려, 보통 120초 동안 6~12기압 정도의 압력을 유지하도록 하였다. 혈관조영술 이후, 풍성을 제거하고 혈관조영술을 다시 시행하였다.

이후에 Wingspan 시스템을 준비하고 교체 와이어(exchange wire)를 통하여 혈관 부위까지 진전시켰다. 스텀트의 길이가 해당 혈관의 정상적인 길이보다 0.5~1.0 mm 정도 큰 것을 선택하였다. 선택된 스텀트는 혈관형성 번성을 가거나 조금 더 긴 것으로 선택하여 혈관 부위 전체에 걸쳐서 윤리적 방법을 통해 측정하였으며, Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) 연구의 방법론을 적용하여 정상적인 혈관의 표준 길이로 비교하였다. 3 모든 환자는 치료 이전에 항혈소판제(아스피린과 클로리도 그램(clopidogrel))를 복용하였다. 대부분의 환자는 퇴원 시 아스피린(하루 325mg)과 클로리도그램(하루 75mg)을 지방 받았다. 항혈소판제 복용 투여는 이후 혈관조영술 추적 관찰이 이루어지는 시점까지 유지하였다. 혈관조영술 추적 관찰에서 ISR이 발생하지 않은 환자는 대개 클로리도그램 투여를 중단하였다. 모든 환자들은 치료 이후 계속 아스피린(하루 325mg)을 복용하였다.

추적 영상 검사
추적 영상 검사는 138개의 혈관 병변에서 시행되었다. 대부분의 병변(n=109)은 카테터를 이용한 고정적인 혈관조영술로 평가하였다. 일부 사례(n=28)는 CT 혈관조영술로 평가하였 다. 스텀트를 삽입한 전체 부위 및 상하부 혈관이 CT 혈관조영 수술에서 모두 증가하지 않고 잘 관찰되는 경우, 'ISR 없음'으로 평가하였다. 스텀트를 삽입한 부위 혹은 연결한 혈관을 CT 혈관조영술에서 충분히 확인할 수 없는 경우, 카테터를 이용한 혈관조영술을 시행하였다. 단면 영상이 정상이기로 판단되고나 ISR이 의심되는 경우에도 혈관조영술을 시행하였다. 한편
의 사례에서는 MR 혈관조영술만 시행되었다. 

혈관 영상의 추적 검사 시, 내강(luminal)의 최소 직경을 확인하고 측정하였다. 잔류(residual) 혈착 혹은 재발한 혈착은 WASID 기법을 이용하여 그 비율을 계산하였다. ISR은 (1) 50% 초과 혈착(스텐트 내부 혹은 5 mm 이내에 인접한 부위), (2) 20% 초과의 내강 소실인 병변으로 정의하였다. 내강 단면의 측정은 각 기관에 속한 저자에 의하여 이루어졌고, 1명의 연구자(D.J.F)가 재확인하였다. 혈착 병변의 재시술 여부는 각 시술자의 판단에 따라야 한다.

임상적 사항의 관찰

Wingspan 스텐트술 후, 정기적인 임상적 추적 관찰은 휴식 시점, 2~6주, 3~6개월 및 12~15개월 시점에서 이루어졌다. 시술 30일 이내에 발생한 뇌졸중 혹은 사망, 그리고 30일 이후에 발생한 동족 관역 영역의 뇌졸중이 일자 신경학적 결과 변수로 정의되었다. 본 분석을 위하여, 24시간 이상 지속된 출혈 혹은 허혈성 사인을 뇌졸중으로 간주하였다. 신경영상학적 소견과 관계 없이 24시간 이내에 호전된 일시적 신경학적 결 손은 일시적혈관종착(transient ischemic attack, TIA)으로 분류하였다. 뇌졸중의 분류(동측 혹은 반대측)는 가능한 신경 영상 검사 소견을 근거하여 결정하였다. 결과 변수 관찰은 각 참여 기관의 연구자가 수행하였다.

결과

동록된 환자

21개월의 연구 기간 동안, 168개의 두개내 과장경화증 병변 (50~99% 혈착을 가진 158명의 환자가 Gateway-Wingspan 스텐트술을 받았다. 환자들(남성 95명, 여성 63명)의 나이는 33~86세(평균 62.7세)에 분포하였다. 90명(57%)의 환자는 뇌졸중으로 방문하였다. 평균 혈착 정도는 75.2%였으며, 115개 의 병변(69%)은 70~99% 혈착을 보였다. 스텐트 전후에 뇌졸중은 9명(5.7%)의 환자에서 발생하였다. 4명(2.5%)의 환자는 시술 전후에 발생한 뇌졸중으로 인하여 사망하였다.

임상적 추적 관찰

본 동록부에 기록된 158명의 환자 중 147명에서 3개월 시점의 추적 관찰이 가능하였다. 제외된 환자는 일자 결과 변수가 발생하였거나(n=9), 30일 이후에 신경학적 결과 이의의 원인으로 사망한 환자(n=2)였다. 이들 중 총 143명의 환자(97.3%)에서 최소 3개월 이상의 추적 관찰이 시전되었다. 127명 중 110명(86.6%)이 12개월 이상 추적 관찰을 받았다. 동록된 환 자의 평균 임상적 추적 관찰 기간은 14.2개월이었다.

일차 결과 변수의 누적 발생률은 전체 환자에서 15.7%였고, 현저한 혈착(70~99%)을 보이는 환자들에서 13.9%였다. 30일 이후 동측의 뇌졸중률은 발생한 13명 가운데 3명이 사망하였다. 30일 이후 동측의 뇌졸중이 발생한 13명 중 10명(76.9%)이 시술 6개월 이내에 발생하였으며, 12개월 이후에 뇌졸중이 발생한 환자는 없었다. 30일 이후 9명의 환자에서 동측의 TIA가 발생하였다. 30일에서 12개월 사이에 발생한 13명 중 10명(76.9%)은 사망하였다. 12개월 추적 관찰은 100명의 환 자 중 22건의 사례였다.

대부분의 설치술 이후 사망(86%)은 항혈소판제의 중단 (n=6), ISR (n=12), 혹은 두 원인의 중복(n=1)에 기인하였다. 3명의 환자에서는 원인을 밝히지 않았다. 30일 이후 동측의 뇌졸중이 발생하여 이차 결과 변수가 발생한 것으로 판정된 13명의 환자에서, 5명은 ISR, 5명은 항혈소판제의 중단에 기인한 것으로 생각되며, 3명에서는 원인을 밝히지 않았다. 항혈소판제 중단 이후에 발생한 환자에서, 뇌졸중은 시술 후 2~9개월(평균 4.4개월)의 시점에서 발생하였다(Figure 1~3), ISR에 기인한 뇌졸중이 발생한 환자에서, 뇌졸중은 3.5~11.5개월(평균 6.9개월)의 시점에서 발생하였다(Figure 4). 12개월 시점에서 발생한 2명의 환자들이 ISR이나 연관된 뇌졸중으로 발생한 평균 사망 시점과 비슷하여 발생하였다. 이 환자들은 ISR과 관련된 일시적 증상을 경험한 바 있으며, ISR 제한으로 인한 뇌졸중이 발생하기 전에 1회 이상의 혈관형상검사를 받은 환자였다. 원인을 알 수 없는 뇌졸중이 발생한 환자들은 평균 3.2개월 이후(범위, 1.5~5개월)에 뇌졸 중을 경험하였다. 30일 이후 동측의 TIA가 발생한 9명의 환 자들 중 7명은 ISR과 연관되어 있었고, 1명은 항혈소판제의 중단에 기인한 것으로 생각된다. 1명의 환자는 두 가지 요소를 모두 가지고 있었다.
고찰

US Wingspan Registry를 분석한 본 연구에서 가장 중요한 결과는, (1) 일부 환자들은 Gateway-Wingspan 스테트를 사용하여 성공적으로 PTAS를 한 후에도 동족의 허혈성 사건을 경험한다는 점, (2) 이러한 지연성 사건은 항혈소판제의 종류 혹은 ISR 등 일정한 요소에 기인한다는 점, (3) 이는 대개 치료 후 6개월 이내에 발생한다는 점을 들 수 있었다.

Gateway-Wingspan 스테트 시스템은 증상성 두개내 축상 경화증에 대한 새로운 치료법으로, 2005년에 소개되었다. 이 시스템의 도입 초기에는, 약물로만 치료한 고위험군 환자들에 비하여 양호한 시술 전후 뇌졸중 위험(약 5%)을 보이는 것으로 알려졌다. 그러나 스테트 이후 혈관조영술을 통해 혈착 여부를 평가한 두 연구를 중간 분석한 결과, ISR 혹은 완전폐색의 발생률은 25~35%에 이르는 것으로 알려졌다.3,5,6 이 결과를 미리의 Eurasian Humanitarian Device Exemption 연구 결과에 비해 매우 높은 혈착이라고 할 수 있다. ISR이 발생한 환자의 대부분은 무증상이나, 약 1/3에서 동측의 허혈성 증상이 발생하였다.3,5,6 이 때문에 스테트술 이후의 치료 효과 지속성 여부에 대한 의문이 제기되었으며, 성공적으로 스테트를 설치하였다는 하더라도 이후 허혈성 사건이 계속될 가능성이 있다는 의혹이 따랐다. 본 분석의 목적은 바로 이 문제를 규명하기 위한 것이었다.

스테트술 이후의 허혈성 사건 발생률

본 연구에서, 일부 환자들은 PTAS가 성공적으로 시행된 후에도 동족의 허혈성 사건을 경험하였다. 이러한 지연성 증상 발생은 전체 허혈성 사건 수의 약 2/3에 해당하며, PTAS 시술 동안에 발생한 증상 수를 증가시킨다.

Figure 3. Subtracted image from an angiogram performed at 8 weeks demonstrates no significant in-stent restenosis (same patient as in Figure 1).
지연성 혈착성 사건의 발생 시점

대부분(80%)의 지연성 혈착성 증상(TIA 및 뇌졸중)은 심사 후 6개월 이내에 발생하였다. 이러한 지연성 증상의 발생 시점은 두 가지 주요 위험인자와 '위험 기간'과 잘 상응하고 있다. 

혈관조영술 검사를 시행한 ISR이 발생하지 않았다는 것을 확인한 후 클러피드그램을 중단하였다. 따라서 보다 긴장한 임상적 추적 관찰 및 복잡 순응도에 대한 강조를 통하여, 가장 중요한 시기인 첫 90~180일간 혈관조영술을 충분히 복용하도록 할 수 있을 것이다. 본 연구에서 ISR은 1개월 이후에 혈관조영사용을 중단하여 동맥의 지연성 뇌졸중을 발견한 환자는 단 한 명이었으며, 이 환자는 모든 혈관조영사용을 중단하였다고 한다. 

ISR은 모든 스탠드장이 가지고 있는 임상적 현상이었다. 본 연구에서 ISR은 약 40%의 심사 후 뇌졸중 발생과 관련되어 있었다. 또한 등록부에 포함된 대부분의 환자는 심상 임상적 추적 관찰의 일원으로 스탠드에 대한 영상의학적 검사를 받았다. 추적 관찰 기간 동안 ISR이 발생된 경우, 보통 혈관조영사용을 포함 후유군을 지속하였다. 환자에서 새로운 신경학적 증상이 발생하거나 심사 이전보다 더 현저한 혈착으로 진행하는 경우, 혈관조영적 검사를 재검 시행하였다. 하지만, ISR에 의하여 발생한 뇌졸중 개발은 정규 영상의학적 검사, 약물 치료 및 증외적 시술을 통하여 진단되고 치료할 수 있다. 따라서 ISR에 의한 지연성 혈착성 증상을 예방하는 전략은 주로 현재 사용 가능한 치료 도구를 보완하는 것으로 가능한 것으로 생각된다. 이는 약물방출시판(contrast-controlled balloon), 현재의 자가 환장성 스탠드에 약물방출 기능을 부여하는 것, 혹은 혈관내용을 향하여 장기간에 걸쳐 원심력을 가하는 스탠드를 개발하는 것 등이 포함된다.12,13

한계

본 논문이 Wingspan-Gateway 스탠드를 설치하여 가능 오랜 기간 동안 추적 관찰을 시행한 대규모 연구임은 분명하다. 본 연구 역시 중요한 한계를 가지고 있음을 언급하고자 한다. 가장 중요한 한계로 모든 환자들이 12개월까지 추적 관찰을 받지 못하였다는 점을 들 수 있다(13%가 1년 시점에서의 추적 관찰을 받지 못하였다). 추적 관찰을 받지 못한 환자들의 뇌졸중 발생률이 12개월, 혹은 그 이후까지 추적 관찰을 받은 사람들과 동일하다고 할 수 없기 때문에, 이 점이 1년 뇌졸중 발생률
보고하는 데 있어 잠재적인 차우점의 원인이 되겠다고 하겠다.

결론
PTAS가 성공적으로 시술된 이후, 일부 환자는 계속 동측의 혈전성 사건을 경험한다. 이러한 사례의 대부분은 시술 후 6개월 이내에 발생한다. 혈전성 사건은 항혈소관제의 조기 중단, 혹은 ISRI에 기인할 것으로 생각된다.

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References