Intracranial Stenting of Subacute Symptomatic Atherosclerotic Occlusion Versus Stenosis

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Background and Purpose—Limited data are available concerning the outcome of angioplasty/stenting for subacute atherosclerotic intracranial artery occlusion, which is often associated with progressive symptom development in the salvageable brain under ischemic threat due to poor collateral blood supply.

Methods—Among 177 patients who underwent angioplasty and/or stenting for severe symptomatic intracranial steno-occlusion, 26 had subacute atherosclerotic intracranial artery occlusion. Outcome after stenting (N=22) was assessed according to procedural success (return of antegrade flow and residual stenosis ≤50%), adverse event (any stroke or death) rate, and restenosis (>50%) using weighted Cox proportional hazards regression in the overall cohort and in separate subgroups.

Results—Successful recanalization was achieved in 95%. Three adverse events (13.6%) occurred among patients undergoing stenting for occlusion, including 2 major strokes and 1 nonprocedure-related death. Good outcome (modified Rankin Scale ≤2) was achieved in 73%. In the overall cohort, no significant difference was observed between the occlusion and stenosis groups in terms of the risk of adverse events (hazard ratio for the occlusion group, 1.055; 95% CI, 0.29–3.90) or the risk of restenosis (hazard ratio for the occlusion group, 1.2; 95% CI, 0.19–7.72). A trend toward a higher rate of adverse events was observed in older age (>65 years), progressive worsening, balloon-expandable stent, and no history of a preprocedural P2Y12 assay.

Conclusions—In a cohort of patients undergoing angioplasty/stenting for subacute atherosclerotic intracranial artery occlusion, no significant difference in the rates of adverse events was observed. However, several factors, including age, tended to be associated with a higher event rate.

Key Words: intracranial occlusion ■ outcome ■ stenting

A cute stroke secondary to arterial occlusion requires intravenous tissue-type plasminogen activator or intra-arterial recanalization within 3 or 6 hours of symptom onset, respectively.1,2 Prognosis in these patients is dependent on the main cause of the occlusion, for example, cardiac embolism, particularly in patients who present with substantial neurological deficit.3

Patients with thrombotic atherosclerotic plaques may develop progressive occlusion, and this may result in hypoperfusion and regional artery-to-artery embolism within the vascular territory.4 Neurological status in such patients is usually dependent on both the degree of collateral blood supply to the occluded vascular territory and the amount of potentially salvageable ischemic brain tissue, ie, the ischemic penumbra. The amount can be judged clinically by a mismatch in diffusion–perfusion or diffusion–symptom in the ischemic tissue and appears to identify patients with stroke who are more likely to respond to delayed intra-arterial recanalization, that is, recanalization performed beyond the currently recommended 6-hour time limit.5–7

Although the results of extracranial–intracranial bypass for acute and symptomatic severe stenosis or occlusion have been disappointing,8 the findings of the Carotid Occlusion Surgery Study suggest that extracranial–intracranial bypass may be effective in patients with Stage II hemodynamic failure and symptomatic severe stenosis or occlusion.9 However, percutaneous endovascular techniques may prove efficacious for a broader spectrum of patients, because they allow direct correction of hemodynamic insufficiency.10–12

Although there have been several promising reports of endovascular recanalization in cases of extracranial carotid
occlusion, the feasibility of endovascular recanalization for subacute atherosclerotic intracranial artery occlusion (SAIAO) has only been reported anecdotally,\textsuperscript{10-14} and few studies have described the outcome of such cases. Our experience revealed that compared with patients with stenosis, patients with occlusion displayed milder neurological deficit, progressive neurological worsening compared with smaller infarct volume, and longer symptom onset and had considerable salvageable brain tissue. We hypothesized that assuming plaque development in intracranial stenosis has a similar mechanism to that of atherosclerotic occlusion in subacute stroke, the technical feasibility and outcome of intracranial recanalization would be reflected in the finding of a similar risk of adverse events (AEs) in patients with occlusion and stenosis, and this risk would be comparable to that found for stenting. Thus, the aims of the present study were to evaluate technical success and outcome of recanalization in SAIAO and to compare these findings with the results of recanalization in severe intracranial stenosis.

Materials and Methods

Study Population

Data on 177 consecutive patients who were intended to be treated by intracranial angioplasty and/or stenting for symptomatic severe atherosclerotic intracranial stenosis (defined as stenosis of $>70\%$) or occlusion between February 2002 and December 2010 were analyzed retrospectively. The data on stenosis were extracted from the prospective neurointerventional database at Asan Medical Center of the last 3 years. The number of patients in groups of stenosis versus occlusion was 150 versus 27 patients. One patient who underwent stenting 5 months after symptom onset and who had good outcome at 6 months was excluded because he had a history of chronic total occlusion rather than subacute occlusion.

Among 26 patients with SAIAO, 22 patients underwent stenting, 2 patients only underwent balloon angioplasty and 2 patients did not undergo angioplasty or stenting due to the failure of the procedure caused by tortuosity of vessels. Inclusion criteria for SAIAO were: (1) angiographic complete atherosclerotic occlusion of intracranial artery; (2) presentation later than 6 hours after initial onset of symptom; (3) diffusion-perfusion and/or symptom-diffusion mismatch; and (4) border zone cerebral infarct or an infarct secondary to artery-to-artery embolism. Among 150 patients with severe intracranial stenosis, 130 patients underwent stenting, 17 patients underwent balloon angioplasty only, and 3 patients did not undergo angioplasty or stenting due to the failure of the procedure.

Table 1 shows the clinical and angiographic data of patients with intracranial occlusion versus stenosis. The following variables may affect the AE rate and were thus included as possible risk factors: age ($>65$ years versus $\leq 65$ years); sex (male versus female); time interval between symptom onset and stenting ($>1$ versus $\leq 1$ day); initial National Institutes of Health Stroke Scale (NIHSS; $\geq 4$ versus $<4$); presence of vascular risk factors (hypertension, diabetes, hyperlipidemia, smoking, cardiac disease, and history of previous stroke); and lesion location.\textsuperscript{18} For the subgroup analysis of SAIAO patients, the following features were also included: pattern of presenting symptoms (progressive worsening versus stable); lesion location; stent type (balloon-expandable stent [BES] versus self-expandable stent [SES]); and performance of the VerifyNow P2Y12 assay.

There was no industry involvement in the design, conduct, or analyses of the study. The Institutional Review Board of the Asan Medical Center approved the design of the study and the use of clinical data, and all patients provided written informed consent.

Initial Clinical Status and Brain Infarct Lesion Patterns

On admission, neurological status was thoroughly evaluated by an independent neurologist using NIHSS. Initial NIHSS before the procedure ranged from 0 to 29 (median, 5); NIHSS $\geq 8$ (N = 7), $\leq 4$ and $<8$ (N = 10), and 0 to 3 (N = 5). Two groups were identified: (1) a progressive neurological worsening group (N = 9) of patients who required repeat diffusion-weighted imaging due to progression or fluctuation of initial neurological deficit, which revealed a corresponding worsening of the ischemic lesions (Figure); and (2) a stable group (N = 13) who showed no change in neurological deficit. The interval between the 2 diffusion-weighted images in the progressive neurological worsening group ranged between 1 and 4 days (median, 3 days).

Diffusion-weighted and perfusion brain MR images were obtained from all patients before stent placement. None of the patients had a territorial infarct. Main infarct patterns in anterior circulation regions (N = 12) were: border zone (N = 9); localized cortical wedge (N = 2); and perforator (N = 1). Main infarct patterns in posterior circulation regions (N = 10) were: brain stem (N = 7); midbrain and cortical (N = 1); localized cortical wedge (N = 1); and no acute infarct (N = 1).
Angiointerventional Procedures

Antiplatelet and anticoagulation regimens were prescribed to all patients before the procedure. The procedure was performed under monitored anesthesia. During the procedure, each patient received 2000 to 5000 IU of intravenous heparin to attain an activated clotting time of approximately 200 seconds or 2-fold higher than baseline. Additional doses were administered as appropriate, as determined by measurement of activated clotting time. A 5-Fr to 8-Fr sheath (Cook) or guiding catheter (Cordis) was positioned in either the internal carotid artery or the vertebral artery. The side arm of the guiding catheter was flushed continuously with pressurized and heparinized normal saline and was used for angiography. On completion of the angioplasty and stent placement, the patient was administered a daily 75-mg oral dose of clopidogrel for a minimum of 6 months and a 100-mg oral daily dose of aspirin was prescribed for their entire lifespan. For patients regarded as having a long lesion or a stent luminal diameter of ≤2.5 mm, 50 to 100 mg cilostazol twice daily was prescribed for 2 to 6 months.

Recanalization Technique Used to Reopen the Occluded Segment

Under roadmap guidance, a 0.010-inch microcatheter and a 0.014-inch microguidewire were introduced to reach the occluded segment. In most procedures, a Trensend 14 microguidewire was used (Boston Scientific). The occlusion was then probed by careful 1-to-1 movement of the 0.014-inch guidewire. If there was no resistance at the guidewire tip, the occluded segment was smoothly traversed. If there was some resistance at the tip, the guidewire was rotated and turned in the direction of probing to continue the process. The guidewire movement pattern indicates whether the guidewire is situated within the occluded segment or beyond the occlusion. Although the guidewire is in the occluded segment, motion of the guidewire tip is limited during rotation of the guidewire. Once the guidewire has passed the occluded segment, free rotating motion of the guidewire in the vessel lumen can be observed on fluoroscopy. The length of the occluded segment cannot be measured during the initial angiogram because the distal end of the occluded vessel is not visible even after angioplasty. Therefore, the point of freely rotating guidewire movement in the distal lumen can be an important landmark in estimating the position of the end of the occluded segment as well as in measuring the length of the occlusion. Once the guidewire has passed the occluded segment, the guidewire is advanced into the distal cortical vessel as far as possible. Advancement of the guidewire beyond the occlusion is difficult due to the tortuous intracranial vessels and their resistance. Therefore, in most cases, a microcatheter was introduced beyond the occluded segment to follow the guidewire, and the microcatheter was then removed by applying pressure, which was measured using a pressure gauge.

Along the guidewire, a monorail balloon was introduced and balloon angioplasty was performed once or twice using the minimal balloon size (usually 1.5–2 mm) necessary to secure the luminal space and introduce the stent. Before March 2010, BESs were used in all procedures. SESs then became available, and either BES or SES was used during the remainder of the study period. Although there was no specific indication for the use of each stent type, BES was used when the vessel was straight and there was no significant difference in luminal diameter between the proximal and distal occluded arterial segment; and SES was used when the occluded segment was long and tortuous (Figure). BES was used in 14 patients: Drivers (N=8; Medtronic Ireland); 2 patients received 2 stents); Visions (N=4; Guidant); S-670 (N=1; Medtronic Ireland);
and Jostent (N = 1; Abbott Laboratories). SES was used in 7 patients: Wingspans (N = 5; Boston Scientific) and Neuroform (N = 2; Boston Scientific). One patient received both a SES and a BES (1 Winspan and 1 Driver; Figure).

**Clopidogrel Resistance**

The antiplatelet effect of clopidogrel, the most widely used thienopyridine, is variable, and clopidogrel nonresponders have higher rates of ischemic events than responders. The VerifyNow P2Y12 assay first became available in April 2008. Because the luminal diameter of the target intracranial artery in the present study ranged between 0.9 and 3.0 (mean, 1.9), all 7 patients included in the study after this date were screened for clopidogrel resistance before the procedure (230 >P2Y12 reaction units [PRU], N = 3; 230 <PRU, N = 4). Clopidogrel nonresponders (230 >PRU) received additional loading with clopidogrel or an intravenous antiplatelet agent (Reopro or Aggrastat). No adverse event was detected in those 7 patients for whom we managed the resistance after assay.

**Procedural Success and Measurement of Residual Stenosis**

Procedural success was defined as a return of antegrade flow and residual stenosis of <50%. An experienced radiographer, who was blind to the aims of the study, analyzed the angiography results using Quantitative Vascular Analysis (Pie Medical Imaging BV) in accordance with the methods of the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial. The percentage of diameter stenosis, minimal lumen diameter, and reference diameter before and after stent placement were measured. Degree of residual stenosis was determined according to the reference diameter as the most stenotic portion of the lesion between the 2 nonstenotic vessel segments proximal and distal to the stenosis.

**End Points Assessment and Follow-Up**

The primary end points were AEs, that is, death and strokes. All events were identified on the basis of clinical diagnoses assigned by the responsible physician. Death was defined as death from any cause. Stroke, as indicated by the presence of neurological deficits, was confirmed by a neurologist on the basis of imaging studies as previously described. Clinical, angiographic, procedural, and outcome data were collected with the use of Asan Medical Center intranet-based dedicated reporting system. Clinical follow-up after stenting was recommended at 1 month, 6 months, and 1 year and then annually thereafter. For all patients treated with stenting, routine angiographic follow-up was recommended 6 to 12 months after the procedure. However, patients who were at high risk of procedural complications during angiography and who had no symptoms or signs of ischemia as well as patients who declined the recommendation did not undergo routine follow-up angiography (N = 1) and underwent CT angiography (N = 10) or transcranial Doppler ultrasound (N = 1) instead.

Restenosis (>50%) was identified by cerebral angiography according to the WASID method or increased flow velocity on follow-up transcranial Doppler compared with the prestenting Doppler value for the stented vessels. Restenosis on CT angiography was determined by binary estimation (>50%) after delineation of traced-stented vessel segments by Advanced Vessel Analysis (Siemens, Erlangen, Germany) or visual inspection of luminal patency along the stented vessel in conjunction with CT perfusion.

**Statistical Analysis**

Among patients with symptomatic severe intracranial stenocclusion, outcomes were compared between patients with occlusion and patients with stenosis. To reduce the effect of treatment selection bias and potential confounding factors in the present observational study, weighted Cox proportional hazards regression models were constructed using the inverse probability of treatment-weighted method to adjust for significant differences in baseline characteris-

<table>
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BES indicates balloon-expandable stent; SES, self-expandable stent.

*One patient had BES + SES.

**Results**

Procedural success was achieved in 95% (21 of 22) of the patients with SAIAO. The AE rate (any stroke or death) after stenting was 13.5% in the occlusion group and 13.8% in the stenosis group (Table 1). In the overall matched cohort, no significant difference was observed between the occlusion and stenosis groups in terms of the risk of AEs (hazard ratio for the occlusion group, 1.055; 95% CI, 0.29–3.90) or the risk of restenosis (hazard ratio for the occlusion group, 1.2; 95% CI, 0.19–7.72).

Three AEs within 6 months of the procedure occurred among the 22 patients undergoing stenting for occlusion (13.6%). These were 2 major strokes due to occlusion of the stented vessel at 0 and 7 days, respectively and 1 death 44 days after the procedure. The cause of death was regarded as a cardiac origin because the patient with a history of myocardial infarction and atrial fibrillation did well until sudden death at home. The 3 events occurred in patients who were older (>65 years), displayed progressive worsening, had BES, and had not undergone the P2Y12 assay before the procedure. Although no statistical significance was found due to the small sample size, a tendency toward a higher rate of AEs was observed in those patient subgroups with SAIAO (Table 2).

Residual stenosis after stenting was a mean of 24% (0%–64%). Successful return of antegrade flow led to good immediate recovery in 1 patient, although procedural success was not achieved due to significant residual stenosis of 64% after stenting. Two patients did not undergo stenting because good flow was achieved with angioplasty alone with residual stenosis of 19% and 50%.
in each patient and revealed good outcome at 6 months. The recanalization procedure failed in 2 patients due to tortuous cerebral vessels and these patients underwent extracranial–intracranial bypass surgery. One of these patients had a good outcome and 1 patient had a major stroke postoperatively. Final luminal diameter after stenting was 0.9 to 3.0 mm (mean, 1.9 mm) in 22 lesions.

The follow-up period of the 22 patients who had undergone stenting ranged from 6 to 71 months (mean, 25 months). Good final outcome (modified Rankin Scale ≤2) was achieved in 16 of 22 patients (73%) at 6 months. Follow-up data were available for 12 patients. One patient was found to have asymptomatic occlusion of the stented vessel (basilar trunk) on cerebral angiogram 12 months postprocedure. No restenosis was detected in the 11 remaining patients.

Discussion
The present study revealed the outcome of intracranial stenting for occlusion and compared the outcome of intracranial stenting for stenosis in a cohort of patients with severe intracranial steno-occlusive disease. This demonstrated that angioplasty and/or stenting for intracranial artery occlusion is technically feasible and acceptable. Good outcome (modified Rankin Scale ≤2) was observed in 73% of patients within 6 months. The present study also revealed that the risk associated with recanalization was similar to that for stenting. The AE rate for any stroke and death was 13.6% in the occlusion group and 13.8% in the stenosis group, and after propensity score matching, no statistically significant difference was observed between the 2 groups. AEs tended to occur more frequently in patients who were older (>65 years), who displayed progressive neurological worsening, had a BES, and who had not undergone performance of the P2Y12 assay.

Recently, enrollment in the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) study to compare aggressive medical management alone versus aggressive medical management plus angioplasty combined with stenting in patients with symptomatic high-grade (70% to 99%) stenosis of a major intracranial artery has stopped because 14% of patients treated with angioplasty combined with stenting experienced a stroke or died within the first 30 days after enrollment compared with 5.8% of patients treated with medical therapy alone, which represents a highly significant difference. Although the 14% stroke and death rate of the stenting arm in SAMMPRIS was similar to our 13.6% result, our study differs from SAMMPRIS in that it included patients with symptomatic complete intracranial occlusion and in whom 77% showed an initial NIHSS ≥4 and 41% of these patients revealed progressive neurological worsening against medical treatment in a median of 3 days. The stroke and death rate of 5.8% in the medical arm of the SAMMPRIS is comparable to the 4.1% rate of our previous stenting results for stable patients, although our results included only Koreans and might therefore differ in non-Asian.

Acute stroke secondary to cardiac embolism is associated with the development of a sudden and severe neurological deficit. A large territorial infarct may develop if recanalization is not achieved within an appropriate time window. Compared with acute stroke secondary to cardiac embolism or occlusive thrombosis due to a ruptured plaque, SAIAO appears to be associated with border zone, perforator, or scattered cortical infarcts and mismatch in diffusion–perfusion or diffusion–symptoms. However, considering that 77% of patients had NIHSS ≥4 before the procedure, SAIAO might be associated with a poor prognosis due to a tendency toward progressive neurological worsening as was observed in 41% of the present cohort. This suggests the existence of a specific time window for recanalization.

In contrast to whites, intracranial stenosis is more common than extracranial stenosis in Asian populations. Compared with the carotid artery and coronary artery, less histopathologic data are available concerning the nature of preocclusion atherosclerotic plaques in the intracranial arteries, possibly due to their rarity among whites and their relative inaccessibility. However, the adventitia and media of the intracranial arteries are thinner than those of the extracranial arteries, and their internal elastic lamina is fenestrated differently. These differences may contribute, in part, to the different pattern of atherosclerosis in intracranial vessels compared with extracranial vessels of a comparable size. Although luminal stenosis and the lipid core of plaques within the intracranial artery may both contribute to the development of ischemia, histopathologic studies have demonstrated that the fibrous cap of plaques within the intracranial artery was thicker than that of plaques within the coronary and carotid arteries. Several high-resolution MRI studies have shown dense rim enhancement at the plaque, which may suggest the presence of thick fibrous tissue, like in the carotid arteries, which unlikely occurs in ruptured plaque of the coronary artery. Therefore, the present authors hypothesize that SAIAO mainly results from the erosion of pre-existing plaques and the formation of a thrombus.

The current study had several limitations. First, it was impossible to estimate the degree to which resistance to the antiplatelet agent affected the rate of AEs, because the P2Y12 assay was only available for the 7 most recent patients and all of the AEs occurred in patients who did not undergo performance of the assay. Evaluation of antiplatelet resistance is very critical in the recanalization of SAIAO with a poststenting luminal diameter in the range of 0.9 to 3.0 mm (mean, 1.9 mm), as demonstrated by the fact that as many as 25% of patients were resistant to clopidogrel and thus at increased risk of recurrent cardiovascular events. Second, our study is a nonrandomized study with a small sample size. The present sample size was also insufficient to determine whether outcome between the 2 stent types was attributable to the difference in the final luminal diameter. SES is superior to BES in navigating the tortuous intracranial vessels, whereas BES is able to achieve a better final luminal diameter (Figure). BES was only used in the early phase of the study due to the unavailability of SES. The higher rate of AEs among patients treated with BES is partly attributable to the fact that the P2Y12 assay was not available during the early phase of the study rather than because BES is more thrombogenic than SES. Third, the application of protective devices.
to aspirate thrombi remains limited within the context of intracranial artery occlusion due to the small size of the intracranial distal vascular territory. Microembolization from the erosion or rupture of a vulnerable atherosclerotic plaque can be expected during the recanalization of an SAIAO as occurs in 25% of percutaneous coronary interventions. A proximal protection device such as proximal balloon protection may be used in some cases. Fourth, the technical feasibility demonstrated in the present study requires a certain degree of experience, which could be difficult to standardize. The 2 most important technical points are the probing of the occluded segment and the fluoroscopic detection of the lumen at the distal end of the occlusion. Such a procedure may result in serious complications, although no perforation occurred in the present cohort. Because intracranial vessels are typically very tortuous, catheter-supported gentle guidewire probing using 1-to-1 motion is necessary to pass the occluded segment.

In conclusion, percutaneous endovascular recanalization of a SAIAO was feasible, and the risk was comparable to that for intracranial stenting. Adverse events tended to occur more frequently in patients who were older, who displayed progressive neurological worsening, had a BES, and who had not undergone the performance of a P2Y12 assay.

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Disclosures
None.

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