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BACKGROUND AND PURPOSE: There are a few reports regarding the outcome evaluation of balloon-expandable intracranial stent placement (BEICS). The purpose of our study was to evaluate the outcome and factors related to the adverse events (AEs) of BEICS.

MATERIALS AND METHODS: We evaluated 100 consecutive patients who underwent BEICS. We assessed the procedural success (residual stenosis <50%), AEs (minor strokes, major strokes, and death), clinical outcome, and restenosis (>50%) at 6 months. We also analyzed 18 factors including symptom patterns related to AE rate. Symptom patterns revealed 1) stable patients (n = 73) with improving, stationary, or resolved symptoms; and 2) unstable patients (n = 27) with gradual worsening or fluctuating symptoms (National Institutes of Health Stroke Scale [NIHSS] ≥4) within 2 days before stent placement.

RESULTS: The procedural success rate was 99%. Overall, there were 10 (10%) AEs within the 6 months: 4 (4%) minor strokes, 3 (3%) major strokes, and 3 (3%) deaths including a death from myocardial infarction. AE rate was 4.1% in stable and 25.9% in unstable patients. Restenosis at 6 months revealed 0% (0/59). Good outcome (modified Rankin Scale ≤2) at 6 months was 97% (71/73) in stable and 67% (18/27) in unstable patients. Stepwise logistic regression model revealed that symptom pattern (unstable versus stable) was the only significant risk factor (OR, 8.167; 95% CI, 1.933–34.500; P = .004).

CONCLUSION: BEICS revealed a low AE and good outcome rate at 6 months, especially in the stable patients. Midterm outcome was also favorable in the unstable patient group.

Intracranial atherosclerosis is a major cause of ischemic stroke and accounts for 8% to 15% of strokes caused by cerebral atherosclerosis, depending on the population studied.[1,2] The rate of stroke ipsilateral to the intracranial stenosis (50%–99%) is 11% at 1 year and 14% at 2 years, despite the use of either warfarin or aspirin and possible vascular risk factor modifications.[3] Furthermore, the risk for subsequent stroke in the territory of the stenotic artery is 23% at 1 year and 25% at 2 years in patients with severe stenosis of 70% or more.[3-5]

Although successful intracranial artery angioplasty has been attempted,[6-9] the efficacy of angioplasty alone seems limited because of early elastic arterial recoil and the chronic, geometric arterial changes caused by the negative remodeling leading to restenosis.[10,11] The recent advent of new-generation stents with a low profile and high flexibility has allowed stent-assisted angioplasty to be considered as an alternative approach for the treatment of intracranial stenosis.[12-18] However, intracranial stent placement, especially with the use of balloon-expandable stents, has not yet been accepted as a routine procedure for the treatment of intracranial atherosclerosis, undoubtedly because of an insufficient outcome evaluation not only from the randomized controlled studies but also from large case series.[19]

We evaluated the procedural success rate of intracranial stent placement as well as the clinical outcome, including the adverse events (AEs) and restenosis after balloon-expandable intracranial stent placement (BEICS) in 100 consecutive patients. We also analyzed the factors related to postprocedural AEs occurring during the 30-day and 6-month postprocedural periods.

Materials and Methods

Among 125 consecutive patients who underwent intracranial stent placement from the prospectively collected neurointerventional data registry from February 2002 to April 2007, 100 consecutive patients were enrolled for this study. Inclusion criterion for intracranial stent placement was symptomatic, severe (≥70%) intracranial stenosis.

We excluded patients from our study who underwent revascularization with a drug-eluting stent (n = 11); patients with acute onset of symptoms within 6 hours of the study (8 hours for symptoms involving the posterior circulation; n = 6); and patients with incidentally detected, significant, ie, more than 70% intracranial stenosis noted before coronary artery bypass surgery (n = 3) or asymptomatic severe stenosis with decreased ipsilateral perfusion after previous stroke (n = 3); and patients who underwent stent placement followed by the second revascularization session after intra-arterial thrombolysis or angioplasty (n = 2).

Our institutional review board approved this retrospective study. We also obtained written informed consent for the therapy from each patient and their families after we fully explained the nature of the procedure to them.

Patient age ranged from 34 to 80 years (mean, 61 years). There were 78 men and 22 women. Demographic features and risk factors were recorded including hypertension (defined as receiving medication for hypertension or blood pressure >140/90 mm Hg on repeated

Table 1: Summary of potential risk factors studied

Potential Risk Factors	No. of Patients	P Value*
Age (>60 vs ≤60 y)	56 vs 44	1.0
Sex (male vs female)	78 vs 22	.687
Symptom pattern (unstable vs stable)	27 vs 73	.004
Initial NIHSS (≥4 vs <4)	23 vs 77	.313
Presenting symptom (stroke vs TIA)	57 vs 43	1.0
Time from symptom onset (>7 vs ≤7 day)	70 vs 30	.482
Lesion location (anterior vs posterior)	69 vs 31	.277
Degree of stenosis (≥70% vs <70%)	49 vs 51	.049
Length of stenosis (≥7 vs <7 mm)	59 vs 41	.520
Residual stenosis (≥20% vs <20%)	59 vs 41	.086
Presence of diabetes	33	1.0
Presence of hypertension	71	.273
Presence of hyperlipidemia	26	.281
Presence of smoking history	36	.323
Presence of cardiac disease	15	1.0
Presence of previous stroke	32	.722
Level of C-reactive protein (≥0.2 mg/dL)	48	.154
Level of homocysteine (≥15 μmol/L)	28	.426

Note:—TIA indicates transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale.
* Association between adverse event and each independent factor tested by Fisher exact test.

measurements), diabetes mellitus (defined as receiving medication for diabetes mellitus, fasting blood glucose level ≥126 mg/dL, or pancreatic polypeptide 2 level ≥200 mg/dL), cardiac disease, hyperlipidemia (defined as receiving cholesterol-reducing agents or having overnight fasting cholesterol level >200 mg/dL and low-density lipoprotein >100 mg/dL), and current cigarette smoking (current smokers or those who quit smoking <6 months) (Table 1).

Brain MR imaging was obtained in all patients before stent placement. Diffusion-weighted MR images obtained in 85 patients revealed new ischemic lesions in 67: borderzone (n = 21), scattered superficial cortical (n = 15), brain stem (n = 15), deep perforator (n = 5), superficial perforator (n = 5), and wedge-shaped pial (n = 6) lesion patterns of acute ischemic change.[20] Fifteen patients who did not undergo diffusion-weighted imaging had a chronic stage of infarct. Thirty-three patients had no recent brain parenchymal lesions. In 43 patients who presented with a transient ischemic attack, there were no parenchymal lesions in 31 and parenchymal lesions in 12.

Stent placement was performed in the petrocavernous internal carotid artery (ICA) in 35 patients, the M1 portion of the middle cerebral artery in 31 patients, the intracranial vertebral artery (VA) in 20 patients, and the basilar artery (BA) in 14 patients. The number of lesions treated by intracranial stent placement in each patient was either 1 (n = 94) or 2 (n = 6). We used balloon-expandable stents: RX Driver (Medtronic, Minneapolis, Minn) in 68 vessels, Vision (Guidant, Santa Clara, Calif) in 15, Jostent (Abbott Laboratories, Abbott Park, Ill) in 12, Bx SONIC (Cordis, Miami Lakes, Fla) in 7, S670 stent (Medtronic) in 2, Bx VELOCITY (Cordis) in 1, and Express (Boston Scientific, Maple Grove, Minn) in 1.

A complete history was taken of each patient, and a neurologic examination was performed by independent neurologists who were not involved in the interventional procedure. The occurrence of AEs was evaluated at 30 days after stent placement and again at the 6-month follow-up. If a patient was not followed up in an outpatient clinic, an experienced nurse telephoned the patients (n = 24) to evaluate the possibility of any clinically relevant event. The modified Rankin Scale (mRS) was transformed from functional outcome including dependency, living situation, mobility, dressing, and toilet

functions.[21] Ninety-six patients, excluding 3 who died, were clinically followed up for 6 months, including 1 patient who had been lost to follow-up by the time of the 6-month period. Follow-up imaging examination for restenosis at 6 months was done in 59 patients by cerebral angiography (n = 28), transcranial Doppler sonography (n = 21), and CT angiography (n = 10). Restenosis (>50%) was defined on cerebral angiography with the use of quantitative vascular analysis (Pie Medical Imaging, Maastricht, the Netherlands) based on the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) criteria and increased flow velocity on follow-up transcranial Doppler up to the presenting value.[22] Restenosis in 10 patients followed by 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 (n = 7) or on Doppler study below or above the stented vessels (n = 3).

Outcome Evaluation and Risk Factor Analysis
Procedural success was defined as having less than 50% stenosis after the procedure. AEs were defined as minor stroke, major stroke, or death. Minor stroke was defined as a new, nondisabling neurologic deficit or as an increase in the National Institutes of Health Stroke Scale (NIHSS) by 3, but which completely resolved within 30 days.[21] Major stroke was defined as a new neurologic deficit with increased NIHSS by 4 that persisted longer than 30 days. Final outcome at 6 months was determined by mRS (good outcome ≤2, poor outcome ≥3).

In consideration of a wide range of onset of symptoms and presenting symptom patterns in our patients, we categorized our patients into the following symptom pattern groups. The stable patient group included those patients who had resolved, improving, or stationary symptoms before the stent placement procedure. The unstable patient group included patients who had progressive or fluctuating neurologic symptoms (NIHSS ≥4) corresponding to intracranial stenosis within 2 days before the stent placement procedure. We defined medically refractory patients as those who had a repeated symptom despite having received medical treatment for at least 3 days.

We included the following variables that may affect the AE rate as possible risk factors: age (>60 versus ≤60 y), sex (male versus female), symptom patterns (unstable versus stable), initial NIHSS (≥4 versus <4), time interval from onset of symptoms to procedure (>7 versus ≤7 days), presenting symptoms (stroke versus transient ischemic attack), location of lesion (anterior versus posterior circulation = M1 + ICA versus BA + VA), degree of present stenosis (≥70% versus <70%), length of stenosis (≥7 versus <7 mm), residual stenosis after stent placement (≥20% versus <20%), presence of vascular risk factors (diabetes, hypertension, hyperlipidemia, smoking, cardiac disease) including the occurrence of previous stroke, elevated C-reactive protein (≥0.2 versus <0.2 mg/dL), and homocysteinemia (≥15 versus <15 μmol/L).

Angiointerventional Procedures
The patients were premedicated with 100 mg of aspirin and either 75 mg of clopidogrel or 250 mg of ticlopidine at least 3 days before the procedure. All patients were given 200 mg of aspirin and a loading dose of 300 mg of clopidogrel before the procedure, if they were not already taking these medications. We then continued them on 100 mg of aspirin (low-dose regimen) once daily as a permanent medication. In addition, 75 mg of clopidogrel was given once daily for at least 6 months after the procedure. We performed the procedures with the

Table 2: Ipsilateral adverse events related to symptom pattern

Symptom Pattern	No. of Patients	mRS ≤2 at 6 m (%)	Minor Stroke	Major Stroke	Death	No. of Patients With Event	Event Rate (%)	Statistical Difference
			Event					
Stable	73	71 (97)	2	0	1	3	4.1	P = .004*
Unstable	27	18 (67)	2	3	2	7	25.9	
Total	100	89 (89)	4	3	3	10	10	

Note:—mRS indicates modified Rankin Scale.
* Fisher exact test.

patients under local anesthesia after intravenous infusion of midazolam 1.5 to 2.5 mg, or under neuroleptic anesthesia. During the procedure, each patient received 4000 to 8000 IU of intravenous heparin to attain an activated clotting time of more than 250 seconds. Before treatment, diagnostic cerebral angiography was performed via a transfemoral approach. The procedure began with an injection into the common carotid artery followed by selective angiography of both the ICA and VAs.

A 5F to 8F sheath or guiding catheter was introduced and was positioned in either the ICA or the VA. The sidearm of the guiding catheter was continuously flushed with pressurized heparinized normal saline and was used for angiography, according to the treatment steps. After crossing the lesion with a 0.014-inch microguidewire or microcatheter, we placed the balloon catheter over the microguidewire and directed the catheter across the lesion.

We predilated the stenotic lesion by using a balloon catheter with a diameter of 1.5 to 2.5 mm and a length of 10 to 15 mm. Each stent was carefully selected based on the most appropriate availability according to the target vessel size (ie, diameter and length) which was measured on 3D CTA or angiography to avoid oversized stent selection. Residual stenosis of the treated intracranial artery was measured on postprocedural angiography.

An experienced radiographer, who was unaware of the study goal, analyzed the angiographic results by using Quantitative Vascular Analysis (Pie Medical Imaging) based on the WASID methods.[22] The percentage of diameter stenosis, minimal lumen diameter, and reference diameter before and after stent placement were all measured. On completion of the angioplasty and stent placement, the patients received clopidogrel 75 mg orally once a day for at least 6 months and aspirin 100 mg orally once a day for their entire lifespan. Cilostazol 50 to 100 mg twice daily was added for 1 to 6 months in patients who were regarded as having a long lesion or a stent luminal diameter of less than 2.5 mm.

Statistical Methods

We evaluated the event (ie, minor stroke, major stroke, or death), after the procedure as an outcome variable. We performed univariate analysis by using the χ^2 test or Fisher exact test to assess the effect of each independent variable. Independent variables with a P value of less than .05 on univariate analyses were put into a multivariate logistic regression analysis and then were adjusted for age and sex. Stepwise logistic regression analysis incorporating all independent variables was performed to see which independent variables were eliminated and which ones remained as statistically significant prognostic predictors of adverse events. All reported probability values were 2 sided, and P values of less than .05 were considered statistically significant. We performed all statistical analyses by using an SAS version 8.1 (SAS Institute, Cary, NC).

Results

Table 1 summarizes the data related to the demographic, angiographic, and cerebrovascular risk factors. Our procedural success rate was 99%. The overall 10 (10%) AEs within a 6-month clinical follow-up period included 4 (4%) minor strokes, 3 (3%) major strokes, and 3 (3%) deaths including a death from myocardial infarction. All 9 (9%) ipsilateral AEs related to the intracranial stenosis within 6 months developed within the 30-day postprocedural period.

The mean and SD was 69.3% ± 14.4 for the degree of present stenosis and 25.2% ± 16.2 for residual stenosis. There were 73 stable and 27 unstable patients. The number of patients in whom their conditions were medically refractory was 37 (51%) in stable and 20 (74%) in unstable patients.

Being part of the unstable patient group was significantly related to poor patient prognosis on a Fisher exact test (P = .004) (Table 1). The degree of present stenosis was also significantly associated with an increased risk of AEs (P = .049).

Stepwise logistic regression analysis incorporating all independent variables revealed that only the unstable patient group had a significantly higher risk for AEs than the stable group (OR, 8.167; 95% CI, 1.933–34.500; P = .004). In the multivariate logistic regression model incorporating symptom patterns and degree of present stenosis while adjusting for age and sex, only the unstable patient group had a significantly higher risk for AEs than the stable group (OR, 6.237; 95% CI, 1.328–29.306; P = .020).

The stable patient group experienced 3 AEs, in contrast to 7 AEs in the unstable patient group (Table 2). There were 5 of 6 major AEs (ie, major stroke plus death) that occurred in the unstable patient group. Three major strokes were related to reocclusion caused by subacute thrombosis after M1 stent placement (n = 2) after discharge (8 and 9 days after the stent placement procedure), and after VA stent placement (n = 1) before discharge (5 days after the stent placement procedure). Reocclusions related to subacute thrombosis were noted in 2 patients in whom a Jostent (Abbott Laboratories) was placed in the M1 and in 1 patient in whom a Driver (Medtronic) was placed in the VA.

Three deaths were related to hemorrhage after BA stent placement in 2 patients and a myocardial infarction in 1. Death related to myocardial infarction occurred in a 78-year-old patient in the unstable group 22 days after successful intracranial stent placement of the petrous segment and angioplasty of the supraclinoid segment of the ICA.

Follow-up study at 6 months for restenosis was completed in 59 patients. Angiographic follow-up in 28 patients revealed stenosis of a mean 34% ± 0.19 SD. No definite restenosis was

seen on CTA and Doppler study, therefore indicating no re-stenosis in our study patients (0/59).

Discussion

Our study revealed that BEICS can lead to a good outcome (mRS ≤2) in 97% of stable patients and 67% in unstable patients. The overall AE rate after intracranial stent placement within the 30-day postprocedural period was 10% (9% ipsilateral AE rate). When we assessed the results according to the presenting symptom groups, our study surprisingly revealed a difference in the AE rate between the 2 presenting symptom pattern groups after intracranial stent placement (ie, the symptom patterns in the stable group showed only a 4.1% AE rate, whereas the AE rate of the symptom patterns in the unstable group was 25.9%). To the best of our knowledge, this is the first report to demonstrate a very low risk for BEICS in stable patients as well as the existence of a high-risk patient group for intracranial stent placement.

In some aspects, our results correspond to the high-stroke risk in patients enrolled early (≤17 days) in the WASID study (15% versus 8% during 1 year for ipsilateral stroke)[3] and the report of Thijs et al,[23] in that patients whose symptomatic intracranial atherosclerosis failed antithrombotic therapy had a very high rate of cerebral ischemic events (55.8%), ie, 29 of their 52 study patients. Gupta et al[16] also reported a high rate of complications up to 50% in urgent revascularization of acute symptomatic intracranial stenosis by stent placement and thereby suggested that patient selection, procedure timing, and periprocedural medical treatment are critical factors for reducing periprocedural morbidity and mortality.

The stable patients in our study may have had a more favorable natural clinical course than the unstable patients after the events at the time of symptom onset because the 1-year-ipsilateral stroke risk in patients with more than 70% stenosis is 22.5%, whereas the 2-year cumulative risk is 24.6% according to the WASID subgroup analysis,[3] thus indicating only a 2.1% per year risk for stroke if the patients were stable for 1 year after the qualifying event. However, the period of symptom onset in our study between the qualifying event (onset symptom) and stent placement was a mean of 36 days (range, 1–180 days) in stable patients and a mean of 11 days (range, 1–60 days) in unstable patients. In consideration of the 1-year ipsilateral stroke risk of 22.5% in the WASID trial, the 4.1% event rate in our patients is still much lower than that of the WASID trial, at least during the first year.

The Stent placement of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) study showed that the frequency of stroke in the territory of a stented intracranial artery was 7.2% at 30 days and 10.9% at 1 year after the stent placement.[24] Although use of balloon-expandable coronary stents is not permitted in the United States, the recent study with the Wingspan stent system (Boston Scientific), a self-expandable stent, showed ipsilateral stroke or death rates of 4.5% at 30 days and 7% at 6 months.[25] Another Wingspan study revealed that major periprocedural complication rates reached up to 6.1% at 30 days including a mortality rate of 4.9%.[26]

In consideration that the Wingspan studies and SSYLVIA included only stable patients for at least 7 days after a stroke[24,25] and SSYLVIA also included 29.5% extracranial vertebral arterial lesions, the AE rate in the stable symptom pattern group was low in our study. Our results cannot be directly compared with those of either of these previous studies because of our shorter follow-up period, the retrospective nature of our study, and our data are from a large, single-center experience performed primarily by a highly experienced specialist in this field. However, our study does provide evidence that BEICS can be safely performed with a low AE rate.

Although the increased event rate in the unstable patient group may be related to many undetermined factors, we attribute the high rate of major AEs in the unstable patient group compared with the stable patient group, in some aspects, to subacute thrombosis or hyperperfusion,[27] which might be regarded as 2 major complications leading to major AEs within the 30-day postprocedural period in our data.[28,29] Insufficient control of risk factors or antiplatelet medication before intracranial stent placement may also have contributed to the high event rate in our unstable patient group.[30,31] Several procedural and patient factors have been shown to predict the occurrence of subacute stent thrombosis, including longer length of the stent, smaller minimum luminal stent diameter, persistent dissection, and multivessel intervention.[32] However, it is noteworthy that characteristics of the lesion, including length and degree of stenosis which were significant in intracranial angioplasty, were not related to the outcome of intracranial stent placement in our study.[33]

We assume that unstable patients seem to have either unstable plaque in a hemodynamically unstable condition or a hypercoagulable status.[34] Therefore, stabilization of the lesion by medication, including an antiplatelet agent, statin, or angioplasty, followed by a second-session stent placement, may improve the outcome of the unstable group of patients.[15] Because of the emergent nature of the procedure in unstable patients, a loading dose of aspirin 100 mg orally, clopidogrel 300 mg orally (or 600 mg orally, unless there is significant early ischemic change leading to hemorrhage) at least 3 hours before the procedure, and a statin (80 mg of atorvastatin) at a mean of 12 hours before the procedure may improve clinical outcome by improvement of endothelial function, vasodilation, direct antithrombotic effect, and anti-inflammatory actions.[35] An adjunctive platelet glycoprotein IIb/IIIa receptor inhibitor such as tirofiban or abciximab may be used as a rescue management in cases of procedure-related thrombosis. Additional randomized controlled studies will be required for more effective management of such unstable patients.

There were 2 deaths among the 14 stent placement procedures of the BA in our study that were related to hemorrhage. Although the overall mortality rate was 3%, this is certainly high (14.2%) in a single vascular territory. In addition to hyperperfusion or anticoagulation problems, perforation of the vessel wall related to the balloon or to microguidewire manipulation could also be possible causes. Such technical problems or insufficient periprocedural management may suggest the existence of a learning curve of the complicated intracranial stent placement procedure because 4 of 5 major AEs, including 2 deaths, occurred in the first 50 patients in our study. The patient who underwent ipsilateral concomitant stent placement and such a complex procedure might have increased the risk for an adverse procedural outcome. Therefore, we do not believe that this high mortality is solely related to the particu-

lar vascular territory of the basilar artery group, though a further subgroup study would be necessary to prove this assumption.

Our study revealed that all AEs developed 1 month after intracranial stent placement and that there was no recurrence of stroke within 6 months after stent placement. Although follow-up was not complete and cerebral angiography follow-up was obtained only in 28 patients in our study, it was surprising that there was a 0% (0/59) restenosis rate of balloon-expandable stent placement compared with the 33% restenosis rate of SSYLVIA. Symptomatic recurrence seemed to be low in our study after intracranial stent placement, in contrast to SSYLVIA in which the frequency of stroke was 10.9% during the first postprocedure year.[24] Additional follow-up studies will be required to evaluate the rate of restenosis as well as recurrence of symptoms.

The limitation of our study was that factors related to the AE were not prospectively analyzed. Prospective randomized studies may further elucidate the prognosis of the different presenting symptom patterns because the prognosis of the unstable patients can be much worse than that of stable patients unless the intracranial stenosis was relieved by stent placement.

Conclusion

Stent placement of intracranial arteries has a high initial procedural success rate (99%) and acceptable AE rate (10%) in our study. The AE rate was much lower in the stable patient group (4.1%) compared with the unstable patient group (25.9%), thus demonstrating that BEICS can be safely performed in stable patients and the AE rate of intracranial stent placement should be evaluated differently in unstable patients.

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