Intracranial Stenting for Severe Symptomatic Stenosis: Self-Expandable versus Balloon-Expandable Stents

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Summary

Intracranial atherosclerosis against optimal medical treatment requires reperfusion therapy to improve the clinical outcome. We compared outcomes between self-expandable stent (SES) and/or balloon-expandable stent (BES) and present the potential advantages of using each stent.

During the same time frame before and after Wingspan introduction to our institute, 115 consecutive patients underwent intracranial stenting for symptomatic severe intracranial stenosis against optimal medical treatment using BES alone (n = 71) vs. BES or SES (n = 44). We analyzed 15 factors including outcome related to an adverse event (AE), modified Rankin Scale (mRS) and restenosis at six months and retrospectively compared the potential advantages of using each stent.

BES or SES groups had a significantly lower AE rate (2.3%) than the BES only group (14%) (P = 0.049) revealing mRS of ≤ 2 in all patients at six months compared to 93% of the patients in the BES group. Analysis of BES or SES subgroups revealed that BES was associated with less residual stenosis after stenting than SES (18 vs. 32%; P < 0.001).

Both SES and BES can improve the clinical outcome of intracranial stenting especially with a selective choice of SES or BES. Further study is needed to analyse the difference in long-term outcome and the restenosis rate between SES and BES.

Introduction

Atherosclerotic intracranial stenosis accounts for 8–10% of all ischemic strokes in whites; it also causes up to 60% of the ischemic strokes in Asians [1-4]. Patients with symptomatic lesions with ≥70% luminal narrowing and the event occurring within two weeks appear to have a 23% risk for subsequent events at one year despite being on adequate antiplatelet or anti-coagulation therapies [5].

The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial showed that angioplasty and stenting does not add any benefit to aggressive medical treatment alone [6].

Nevertheless, intracranial atherosclerosis that is against optimal medical treatment still requires reperfusion therapy to improve the clinical outcome [7-9].

Because some institutes still use balloon-expandable stent (BES) since the Wingspan stent was introduced, the choice of the most appropriate stent for atherosclerotic intracranial stenoses has not been well established at least in the countries using both BES and a self-expandable stent (SES) [10-12].

The aims of the present study were to evaluate outcomes including the adverse event (AE) rate of SES or BES stenting and to compare them to those of a historical control in which only BES was used.

Materials and Methods

Patient Groups

Between January 2007 and June 2011, patients with severe (≥70%) symptomatic intracranial stenosis underwent intracranial stent placement and were retrospectively analyzed from a prospectively collected database in the neurointerventional data registry. Patients underwent stenting if transient ischemic attacks (TIAs) or stroke occurred despite optimal medical management with antiplatelet therapy (aspirin 100 mg and/or clopidogrel 75 mg/daily), one statin medication, blood pressure control using one or a combined medication from each major class of antihypertensive agents, i.e. diuretic, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, long-acting calcium channel antagonist, potassium-sparing diuretic, vasodilator, and central alpha agonist, and management of secondary risk factors including diabetes, non–high-density lipoprotein [non-HDL], smoking, weight, and exercise, by each physician responsible for the patient [13]. The inclusion criteria for intracranial stent placement were symptomatic, severe (≥70%) intracranial stenosis that was against optimal medical treatment. We excluded those who underwent stent placement followed by a second revascularisation session after intra-arterial thrombolysis [14] or angioplasty; those who underwent revascularisation with a drug-eluting stent or other self-expanding stents such as Neuroform (Boston Scientific Neurovascular, Fremont, CA, USA) and Enterprise (Cordis Neurovascular, Miami Lakes, FL, USA); those with occlusion [8] or tandem lesions; and those with other causes of stenosis including vasculitis or dissection [15]. The reason for excluding other stent usage and other lesions including tandem stenosis was because those patients can have different clinical outcomes as previously reported [16].

The BES only group consisted of 71 patients who underwent intracranial stenting with BES from January 2007 until December 2009. The SES or BES group consisted of 44 patients who underwent stenting by using BES or SES from December 2009 until June 2011. Up until January 2010, BES was the only stent available in our institute. Two operators were retrospectively asked why they had decided to select an SES rather than a BES, or *vice versa*. The questions asked to make a choice of stent selection included one of the following answers: tortuousness of the cerebral vessels that precluded the proper navigation of a stenting device [18]; proximal *vs*. distal luminal discrepancy to the stenotic lesion (conformability of the stent to the vessel); the presence of a side branch such as a perforator in the stenotic lesion that raised the possibility of perforator occlusion due to a snow-plough effect and lesion length.

The risk factors and outcomes of these two groups are shown in Tables 1 and 2. The variables which may affect the AE rate were included as possible risk factors: sex (male vs. female); age (>65 vs. ≤65 years of age); time interval between symptom onset and stenting for patient stability (≤7, ≤30 vs. >30 or >2 vs. ≤2 days) [18]; initial National Institutes of Health Stroke Scale (NIHSS; ≤4 vs. <4); presenting symptom pattern [TIA vs. stroke]; presence of vascular risk factors (hypertension, diabetes, hyperlipidaemia, smoking, cardiac disease, and history of previous stroke); and lesion location [8,11].

Initial Clinical Status and Brain Infarct Lesion Patterns

On admission, the neurological status of each patient was thoroughly evaluated by an independent neurologist using NIHSS. The initial NIHSS before the procedure ranged from 0 to 12 (median, 1). Of the 115 patients, 72 (63%) exhibited an acute infarct on diffusion-weighted images before the procedure. For the 50 patients with infarcts in anterior circulation regions, the main infarct patterns were: border zone (n = 23); territorial infarct, localised cortical wedge or scattered lesions (n = 20); and perforator (n = 7). For the 22 patients with infarcts in the posterior circulation region, the main infarct patterns were: territorial infarct, localised cortical wedge or scattered lesions (n = 16); brain stem or perforator infarcts (n = 6).

Angiointerventional Procedures

Antiplatelets with at least 300 mg of clopidogrel or 200 mg of aspirin were additionally medicated before the stenting procedure if the patients had only one antiplatelet agent. The procedure was performed under conscious monitored anaesthesia with blood pressure monitoring by arterial line. During the procedure, each patient received 2000 to 3000 IU of intravenous heparin to attain an activated clotting time of approximately 200 seconds or twofold higher than baseline. Additional doses were administered as appropriate, as deter-

Table 1 **Summary of risk factors and outcomes in BES vs. BES or SES groups.**

Variables		BES group (n =71)	SES/BES group (n = 44)	Total (n = 115)	p-value
Gender (male)		49 (69%)	34 (77%)	83	0.337
Age (> 65)		59.4 ± 10.3	60.4 ± 9.7	59.8 ± 10.1	0.588
Symptom onset	≤7 days	9 (13%)	8 (18%)	17	0.704
	≤30 days	41 (57%)	23 (52%)	64	
	>30 days	21 (30%)	13 (30%)	34	
Initial NIHSS (≥4)		17 (24%)	8 (16%)	25	0.467
Presenting symptom pattern	Stroke	42 (58%)	30 (68%)	72	0.331
	TIA	29 (41%)	14 (32%)	43	
Risk factors	Hypertension	52 (73%)	33 (75%)	85	0.834
	Diabetes mellitus	26 (36%)	18 (41%)	44	0.645
	Hyperlipidaemia	21 (29%)	20 (45%)	41	0.084
	Smoking	27 (38%)	13 (30%)	40	0.353
	Cardiac disease	15 (21%)	6 (13%)	21	0.312
	Previous stroke	29 (41%)	10 (23%)	39	0.046
Location	Intracranial ICA	16 (22%)	10 (23%)	26	0.193
	M1	29 (41%)	22 (50%)	51	
	Intracranial VA	13 (18%)	10 (23%)	23	
	Basilar artery	13 (18%)	2 (4%)	15	
mRS (≤2) at 6 m		66 (93%)	44 (100%)	110	0.154*
Adverse event in 6 m	10 (14%)	1 (2.3%)	11	0.049*	

SES = *self-expandable stent,* BES = *balloon-expandable stent,* NIHSS = *National Institutes of Health Stroke Scale,* TIA = *transient ischemic attack,* ICA = *internal carotid artery,* VA = *vertebral artery,* mRS = *modified Rankin Scale,* m = *months.*

mined by measuring the activated clotting time. A 5-Fr to 6-Fr guiding catheter was positioned in either the internal carotid artery or the vertebral artery. Balloon angioplasty was performed using a balloon with a smaller diameter than the vessel and the minimum length required to cover the lesion and was followed by stenting. We used Driver (Medtronic Ireland, Minneapolis, MN, USA) (n = 62), Vision (Abbott Vascular, Santa Clara, CA, USA) (n = 9) in the BES group (n = 71) and Driver (n =18), Vision (n = 5), Wingspan (Boston Scientific, Fremont, CA, USA) (n = 21) in the SES/BES group (n = 44).

On completion of the angioplasty and stent placement, the patient was administered a daily 75 mg oral dose of clopidogrel for a minimum of six months and a 100 mg oral daily dose of aspirin was prescribed for their entire lifespan. For patients who had a long lesion or a stent luminal diameter of <2.5 mm, 50 to 100 mg cilostazol twice daily was prescribed for two to six months. The antiplatelet effect of clopidogrel, the most widely used thienopyridine, is variable, and clopidogrel nonresponders have higher rates of ischaemic events than responders [19]. Since the VerifyNow P2Y12 assay first became available in April 2008, about 50% of patients in the single stenting group did not undergo P2Y12 assay whereas antiplatelet resistance was performed in all patients in the elective stenting group. Clopidogrel nonresponders (230 >PRU) received additional loading with clopidogrel.

Definition of Procedural Success and Measurement of Residual Stenosis

Procedural success was defined as successful deployment of a stent with residual stenosis being <50%. An experienced technologist, blind to the aims of the study, analysed the angiography results by using Quantitative Vascular

Table 2 **Summary of risk factors and outcomes of patients in the SES/BES group who received a SES or a BES.**

Variables		SES (n = 21)	BES (n = 23)	Total (n = 44)	p-value
Gender (male)		17 (81%)	17 (74%)	34	0.724
Age (> 65)		5 (24%)	6 (26%)	11	0.862
Symptom onset (≤2 days)		2 (9%)	0 (0%)	2	0.222
Initial NIHSS (≥4)		5 (24%)	3 (13%)	8	0.448
Presenting symptom pattern	Stroke	14 (66%)	16 (70%)	30	0.837
	TIA	7 (33%)	7 (30%)	14	
Risk factors	Hypertension	18 (86%)	15 (65%)	33	0.117
	Diabetes mellitus	7 (33%)	11 (48%)	18	0.388
	Hyperlipidaemia	12 (57%)	8 (34%)	20	0.137
	Smoking	7 (33%)	6 (26%)	13	0.599
	Cardiac disease	5 (24%)	1 (4%)	6	0.088
	Previous stroke	3 (14%)	7 (30%)	10	0.287
Location	Intracranial ICA	0 (0%)	10 (43%)	10	0.001
	M1	17 (81%)	5 (22%)	22	<0.001
	Intracranial VA	3 (14%)	7 (30%)	10	0.287
	Basilar artery	1 (5%)	1 (4%)	2	1.000
Adverse event in 6 m		1 (5%)	0 (0%)	1	0.477
mRS (≤2) at 6 m		21 (100%)	23 (100%)	44	–
Residual stenosis		4-47(32)	0-47(18)	0-47(25)	<0.001
Restenosis		4/9 (44%)	1/10 (10%)	5/19	0.327

SES = *self-expandable stent,* BES = *balloon-expandable stent,* NIHSS = *National Institutes of Health Stroke Scale,* TIA = *transient ischemic attach,* ICA = *internal carotid artery,* VA = *vertebral artery,* mRS = *modified Rankin Scale,* m = *months.*

Analysis (Pie Medical Imaging BV, Netherlands) in accordance with the methods of the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial before and after stenting [8,11]. The percentage of diameter stenosis, minimal lumen diameter, and reference diameter were measured.

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 [11].

End Points Assessment and Follow-up

The primary endpoints were AEs, namely death and strokes at one and six months. The secondary endpoints were the outcomes at six months as measured by the modified Rankin Scale (mRS), and restenosis during the follow-up period. All events were identified on the basis of clinical diagnoses assigned by the responsible neurologists..

Death was defined as death from any cause. Stroke, as indicated by the presence of neurological deficits, was confirmed by independent neurologists on the basis of imaging studies as previously described [8,11].

Clinical follow-up after stenting was recommended at one month, six months, and one year and then annually thereafter. For all patients, routine angiographic follow-up was recommended six 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 ischaemia as well as patients who declined the recommendation did not undergo routine follow-up angiography; instead, these patients underwent CT angiography or transcranial Doppler ultrasound.

Statistical Analysis

Among patients with severe intracranial stenosis, outcomes were compared between two patient groups. Baseline characteristics were summarized for patient groups as number (percentage) for categorical variables and as mean ±SD for continuous variables. Differences were compared using the t test or Mann-Whitney U test for continuous variables, and $\chi 2$ test or Fisher exact test for categorical variables, as appropriate. All reported probability values were two-sided, and a probability value <0.05 was considered statistically significant. SAS software, Version 9.1 (SAS Institute, Inc, Cary, NC, USA) was used for the statistical analyses.

Results

Table 1 shows the baseline characteristics including stroke risk factors of the study patients and outcomes according to the treatment approach in the matched cohort. There was no significant difference between the BES and SES groups for any covariate of risk factors. When we analyzed the two patient groups who underwent stenting procedure, the SES or BES group showed a lower AE rate than the BES only group ($P = 0.049$, Fisher's exact test).

In the SES or BES group there was a preference of stent used according to the lesion location; BES was more commonly used in the intracranial segment of the ICA ($P = 0.001$) and SES in M1 ($P < 0.001$) (Table 2).

One patient who presented with a deep border-zone infarct underwent Wingspan stenting in the right M1 and had a minor stroke eight days after stenting (Table 2). The minor stroke was related to localized haemorrhage regarded as hyperperfusion at the frontal lobe which was subsequently followed by localised cortical infarction due to cessation of the antiplatelet agent. His neurologic deficit was improved and he was able to walk at discharge and his mRS was 2 at six months. All AEs occurred within one month after procedure. There was no additional AE for two to six months of follow-up in either group. There was also significantly less residual stenosis after stenting with BES (18%) than after stenting with Wingspan (32%; $P < 0.001$). The patients in the SES/BES group all had good outcomes (mRS scores of ≤ 2) at six months compared to 93% in the single stent group ($P = 0.154$).

Discussion

The present study revealed that the SES or BES group had a better outcome (AE rate of 2.3%) than when the only choice available was BES (AE rate of 14%). Despite the fact that patients with higher initial NIHSS were included in the present series (24% of the patients had initial NIHSS ≥4), the AE rate of our BES only group (14%) was similar to the AE rate of the SAMMPRIS group (14.7%), in which only the Wingspan stent was used. Because an AE rate of only 2.3% in the SES or BES group is lower than the AE rate of aggressive medical treatment (5.8%) [6], SES or BES stenting could improve the outcome of intracranial stenting and reduce the rate of recurrent ipsilateral stroke in patients with ipsilateral ischaemic events in high-grade stenosis (70%-99%) so that perioperative stroke and/or death in patients treated with PTAS can be reduced to less than 4% to warrant intracranial stenting [9].

Analysis of SES or BES in the present study revealed a certain preference, namely, that BES was more commonly used in the intracranial segment of the internal carotid artery and the intracranial segment of the vertebral artery. By contrast, SES was more commonly used in M1 segments in which the stenosis also extended to the terminal segment of the internal carotid artery or involved the origin of perforators such as the lenticulostriate arteries. Preference for a certain stent type according to the lesion location needs to be studied further.

Although the patient's vascular tortuosity can be evaluated by angiography, vessel wall resistance can only be experienced during the interventional procedure [20]. Such procedure-related factors are difficult to assess in comparative studies. In addition, the designs of SES and BES may have different protective effects regarding perforators arising from the stenotic segment. Because BES is deployed with a balloon, it can cause perforator occlusion due to a snow-plough effect leading to perforator infarct at least in 3% [21]. The patients with preoperative perforator infarct have a significantly higher perforator stroke frequency (8.2%) after BES stenting, compared with the patients without preoperative perforator infarct (0.8%) [21,22].

This study had several limitations. First, it included a relatively small number of patients in a single institute even though we used historical controls from the same institute. Second, our patients in the SES or BES group were

screened for clopidogrel resistance using P2Y12 assay before the procedure. By contrast, only about 50% of the BES group patients were similarly tested. Thus, it remains possible that the higher AE rate of the BES stent group (as in the SAMMPRIS Wingspan group) may reflect a higher rate of antiplatelet resistance in the patient population. Therefore, if antiplatelet resistance testing had been conducted uniformly for all groups, the AE rates of the single stent group in our study may have been different. Third, the restenosis rate was not completely evaluated in our study even though there was a significant difference in residual stenosis between BES and SES after stenting and a rather high incidence of restenosis in the SES group. Further comparative study is required to establish whether the restenosis rate is significantly lower in the BES group. Fifth, together with the significant technological improvement after December 2009 in the catheter and wire, the stent itself, and the deployment system may also have had at least some role in improving the outcome of intracranial stenting. Technical problems like device failure or vessel perforation, and insufficient periprocedural management related to hyperperfusion, anticoagulation or antiplatelet medication may suggest a learning curve for the complicated intracranial stent placement procedure, especially in the first 50 patients [11,23].

In conclusion, intracranial stenting can affect clinical outcome since it contributes to lower the rate of adverse events. To determine whether particular stent types are associated with better long-term outcomes or restenosis compared to other devices, further long-term follow-up studies should be performed.

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