ORIGINAL RESEARCH

Neuro Elutax SV drug-eluting balloon versus Wingspan stent system in symptomatic intracranial high-grade stenosis: a single-center experience

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ABSTRACT

Background Intracranial atherosclerotic disease is a well-known cause of ischemic stroke. Following the SAMMPRIS trial, medical treatment is favored over stenting. Drug-eluting balloons (DEB) are widely used in coronary angioplasty, showing better results than bare-surface balloons. There is little evidence of DEB employment in intracranial stenosis, especially of paclitaxel-eluted balloons (pDEB). The Neuro Elutax SV (Aachen Resonance) is the first CE certificated pDEB for intracranial use.

Objective To compare pDEB Neuro Elutax SV (ElutaxDEB) with the Wingspan/Gateway stent system (WingspanStent).

Materials and methods A single-center, open-label, retrospective cohort study of 19 patients with symptomatic atherosclerotic intracranial high-grade stenosis treated with either ElutaxDEB or WingspanStent from a tertiary stroke center in Switzerland.

Results Eight patients (42%) received ElutaxDEB. Median clinical follow-up was 10 months for the WingspanStent and 9.5 months for ElutaxDEB (P=0.36). No differences were found in the clinical baseline characteristics, with a median stenosis grade of 80% for the WingspanStent and 81% for the ElutaxDEB (P=0.87). The compound endpoint 'ischemic re-event and/or restenosis' was significantly lower for ElutaxDEB (13% vs 64%; P=0.03, OR 0.08 (95% CI 0.007 to 0.93; P=0.043) than for the WingspanStent.

Conclusions The ElutaxDEB may be a promising alternative treatment for patients with symptomatic high-grade intracranial stenosis showing a significantly lower rate of ischemic re-events or restenosis in comparison with the WingspanStent-treated patients with a similar safety profile. Further studies will be needed to definitively elucidate the role of pDEB in the management of symptomatic intracranial high-grade stenosis.

INTRODUCTION

Intracranial atherosclerotic disease (ICAD) is a well-known cause of stroke and is responsible for approximately 5–10% of all strokes and up to 50% in the Asian population, with an estimated 1-year stroke-free survival rate of 88%.[1] Despite best medical care, the annual risk of recurrent stroke in symptomatic ICAD is around 9–12%.[2] Therefore, ICAD has to be regarded as a serious medical condition with a high risk of strokes. In order to improve the poor outcome in ICAD, endovascular revascularization using percutaneous transluminal angioplasty with stenting (PTAS) was developed in the 2000s.[3 4] As a result of the SAMMPRIS trial[2], medical treatment rather than stenting is regarded as first-line therapy because of the high incidence of periprocedural complications (14.7%).[5] Restenosis is an additional major drawback in stent-treated patients, with a recurrence rate of up to 34%. In the post-SAMMPRIS era, there is still a debate about stenting as a possible alternative treatment,[6–8] because despite best medical treatment recurrence rates in symptomatic high-grade stenosis are still considerable.

Following the first randomized clinical trial (RCT) in 2006,[9] recanalization using drug-eluting balloons (DEB) became a well-established technique in coronary angioplasty. However, there is little evidence for the deployment of DEB in ICAD. Several single-center case series have shown the technical feasibility and safety of different drug-eluting stents or DEB.[10–13] Several different DES are available, such as Cipher (Cordis, Miami Lakes, Florida, USA), Taxus Express (Boston Scientific, Natick, Massachusetts, USA) or the Endeavor (Medtronic, Minneapolis, Minnesota, USA), which are not primarily designed for neurovascular procedures and therefore considered off-label use.[14] The Neuro Elutax SV (Aachen Resonance) is a CE certificated, hydrophilic balloon— specifically designed for neurovascular application—with an even 360° coating of 2.2 µg/mm^2 paclitaxel, a highly hydrophilic anticancer drug (figure 1).

The aim of this study was to assess the feasibility, safety, and efficacy of PTA/Neuro Elutax SV DEB compared with PTAS using the WingspanStent system in patients with high-grade ICAD.

MATERIALS AND METHODS

Patient selection

This retrospective study with an open-label cohort design was carried out at a tertiary stroke center and approved by the local ethic committee.

We initially identified 40 patients with symptomatic intracranial high-grade stenosis who had been treated endovascularly at our institution between January 2009 and September 2016. Endovascular treatment was indicated in patients with symptomatic high-grade intracranial artery stenosis (≥70% in conventional cerebral angiography) with

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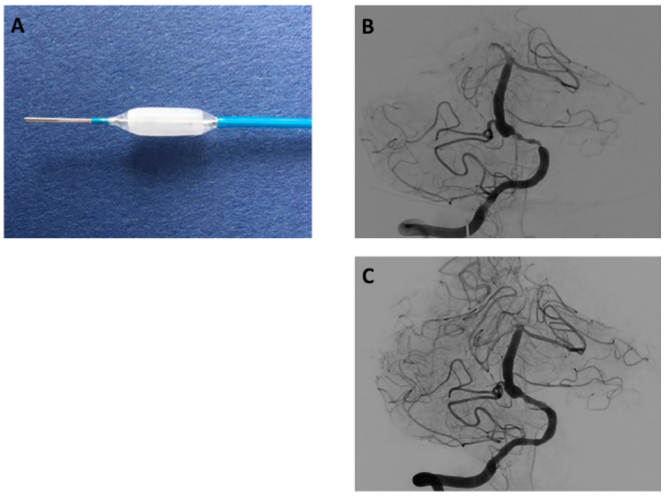

Figure 1 (A) Neuro Elutax SV balloon catheter—CE certificated—specifically designed for neurovascular applications, with a 360° coating of paclitaxel, a common anticancer drug inhibiting intimal hyperplasia. (B,C) Illustrative case of a patient with a symptomatic right-sided V4 segment 70% stenosis of the vertebral artery treated with the Neuro Elutax SV; before (B) and after (C) procedural cerebral angiography. A reduction of stenosis from 70% to 20% was achieved.

recurrent or progressive stroke/transient ischemic attack (TIA) despite medical treatment. Most patients had at least one platelet inhibitor or oral anticoagulant and received high-dose statins. Furthermore, lifestyle modification and/or drug treatment was established for reduction of risk factors for secondary stroke prevention.

All eligible patients had to be over 18 years and were recanalized either with PTA with Neuro Elutax SV paclitaxel DEB or PTAS using the well-described and approved Wingspan stent system consisting of the WingspanStent and Gateway balloon. Patients treated with other stent systems or other device combinations were excluded. This stringent selection process was used to define two homogeneous treatment groups and resulted in 19 patients fulfilling all the above-mentioned criteria (PTA n=8, PTAS n=11).

Procedures

Most of the interventional procedures were performed under general anesthesia (n=16, 84%). All procedures were performed on a Philips Allura Xper FD20/20 biplane angiography system (Philips Medical System, Best, the Netherlands) according to departmental protocol, with intraprocedural modification if required. Briefly, access was achieved through the right common femoral artery, where a 7F long-sheath system was placed. After conventional catheter-based angiography an interventional procedure was performed with the following two device systems: Neuro Elutax SV (Aachen Resonance, Luxembourg)—a CE-certificated DEB specifically designed for neurointerventional procedures—with length 10–30 mm and diameters from 1.5 to 4 mm; and Wingspan stent system (Boston Scientific, Natick, USA) with Gateway PTA balloon catheter (Stryker Neurovascular, Fremont, California, USA)—a Food and Drug Administration approved angioplasty system specifically designed for the neurovascular arteries—as the standard and reference PTAS system.

For the Wingspan stent system the over-the-wire technique was used. The Neuro Elutax SV DEB is a monorail system. Submaximal angioplasty technique was performed for DEB deployment with a balloon inflation time of 30 s.[15]

The decision about which device to use was at the discretion of the neurointerventionalist in charge. Dual antiaggregation with aspirin and clopidogrel was initiated for at least 6 months in all patients treated with PTAS. In patients treated with pDEB Elutax, two patients received therapeutic anticoagulation owing to atrial fibrillation, three aspirin/clopidogrel, and three aspirin alone.

Imaging

The degree of stenosis before and after intervention was determined according to NASCET criteria in cerebral digital subtraction angiography (DSA).[16] The follow-up stenoses were assessed according to the underlined follow-up imaging technique.

Outcome measures

The primary outcome was the compound endpoint of recurrent stroke/TIA and/or restenosis. Restenosis was defined as radiological evidence of postinterventional stenosis of >50% measured by ultrasound, MRI, CT angiography or cerebral angiography during a median follow-up period of 4 months (range 1–9) for the Wingspan and 3 months (range 3–3.5) for the Elutax patients. Any focal neurological symptom related to the corresponding vascular territory occurring within the follow-up period was considered as recurrent stroke or a TIA. Secondary outcomes were stroke or any death within 30 days and good clinical outcome (modified Rankin Scale (mRS) score ≤2) at follow-up.

Statistical analysis

Epidemiological, clinical and radiological data were acquired from the medical records.

All data were anonymized and reviewed by the authors. All statistical analyses were performed by using the STATA/IC 14.1 software (StataCorp LLc, Texas, USA). Study parameters were compared between the two patient groups using either a two-tailed t-test for continuous variables or the Wilcoxon rank sum test for categorical variables. Logistic regression analysis was performed. For all results, a P value <0.05 was considered statistically significant.

RESULTS

A total of 19 patients (9 (47%) female) with 20 lesions (one tandem lesion) were eligible for this study. Eight patients (42%) were treated with a pDEB Elutax SV and; 11 patients (58%) with a Wingspan stent system. The median clinical follow-up was 9.5 months (IQR 4.5–27) for the Elutax patients and 10 months (IQR 6–58) for the PTAS patients, respectively (P=0.36). There were no significant differences in the epidemiological and clinical baseline characteristics between the two groups (table 1). Median age was 68.5 years (IQR 52–76) for the Elutax patients and 67 years (IQR 59–73) for the Wingspan patients (P=0.86). Both groups had similar distributions of vascular risk factors, such as hypertension, diabetes, dyslipidemia, smoking and atrial fibrillation (table 1). Median National Institute of Health Stroke Scale (NIHSS) score was 0 (IQR 0–4) for the Elutax patients and 2 (IQR 0–6) for the PTAS patients (P=0.28). Seventy-five percent of the Elutax patients and 45% of the Wingspan patients had TIAs as initial presenting symptom (P=0.21). Nearly all patients (90%) were on antiplatelet or anticoagulant therapy and received an anti-lipid agent before admission.

Table 1 Demographic, clinical baseline and target lesion characteristics

Characteristics	Elutax (n=8)	Wingspan (n=11)	P value
Gender, female, n (%)	3 (38%)	6 (55%)	0.47
Age (years), median (IQR)	68.5 (52–76)	67 (59–73)	0.86
Clinical follow-up (months), median (IQR)	9.5 (4.5–27)	10 (6–58)	0.36
NIHSS score on admission, median (IQR)	0 (0–4)	2 (0–6)	0.28
Vascular risk factors			
Hypertension, n (%)	6 (75%)	8 (73%)	0.81
Diabetes, n (%)	1 (13%)	4 (36%)	0.26
Dyslipidemia, n (%)	3 (38%)	7 (64%)	0.28
Coronary artery disease, n (%)	4 (50%)	3 (27%)	0.53
Smoking, n (%)	1 (13%)	2 (18%)	0.74
Peripheral artery occlusive disease, n (%)	0 (0%)	1 (9%)	0.39
Atrial fibrillation, n (%)	1 (13%)	1 (9%)	0.82
History of stroke, n (%)	3 (38%)	4 (36%)	0.96
Medication on admission			
Aspirin, n (%)	3 (38%)	7 (64%)	0.27
P2Y12 inhibitor, n (%)	1 (13%)	1 (9%)	0.82
Dipyridamole, n (%)	0	1 (9%)	0.39
Dual antiplatelet therapy, n (%)	1 (13%)	1 (9%)	0.81
Vitamin K antagonist, n (%)	1 (13%)	0 (0%)	0.24
NOAC, n (%)	1 (13%)	0 (0%)	0.24
Anti-lipid agent, n (%)	6 (75%)	6 (55%)	0.51
Severity of stenosis			
Degree of stenosis (%) before intervention, median (IQR)	81% (72.5–92.5)	80% (72–100)	0.87
Degree of stenosis (%) after intervention, median (IQR)	37.5% (20–60)	10% (10–50)	0.23
Localization of target lesions			
Internal carotid artery, n (%)	0 (0%)	1 (9%)	0.39
Middle cerebral artery, n (%)	3 (38%)	5 (45%)	0.74
Vertebral artery, n (%)	3 (38%)	3 (27%)	0.64
Basilar artery, n (%)	2 (25%)	2 (18%)	0.73

IQR, Interquartile range; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; NOAC, novel oral anticoagulant.

The overall severity of stenosis in this study was 80% (median; IQR 75–95). The degree of stenosis was reduced from 81% (median; IQR 72.5–92.5) to 37.5 (median, IQR 20–60) in Elutax patients and from 80% (median, IQR 72–100) to 10% (median, IQR 10–50) in Wingspan patients (P=0.23) (table 1). Localization of the target lesions was quite similar in both groups (table 1).

For the primary outcome (table 2), the compound endpoint of recurrent stroke/TIA and/or restenosis within the follow-up period of 9.5 months for the Elutax and 10 months for the Wingspan patients, respectively, was significantly lower for the Elutax patients (n=1, Wingspan n=7, P=0.03; logistic regression OR=0.08, CI 95%: 0.007 to 0.93, P=0.043). No other correlation with demographic or baseline characteristics was found (data not shown).

No clinical re-events—defined as TIA or stroke in the vascular territory of the formerly treated stenosis within the follow-up period—were reported for Elutax patients, whereas 5 (3645%) of Wingspan patients had new clinical symptoms in the corresponding vascular territory (TIA n=4, minor stroke n=1). Of those patients, four out of five underwent conventional DSA; three of them needed immediate interventional procedure with angioplasty or intra-arterial thrombolysis. Median time to recurrent stroke/TIA was 3 months (IQR 1.5–4) after the intervention.

Table 2 Clinical and technical outcome measures

Outcome measures	Elutax (n=8)	Wingspan (n=11)	P value
Good clinical outcome (mRS score ≤2) at follow-up	5 (63%)	9 (82%)	0.36
mRS score on follow-up, median (IQR)	1 (0-3)	1 (0-2)	0.95
Stroke or death within 30 days, n (%)	1 (13%)	0 (0%)	0.24
Technical success*, n (%)	5 (63%)	7 (64%)	0.96
Transient ischemic attack, n (%)	6 (75%)	5 (45%)	0.21
Compound recurrence rate, n (%)	1 (13%)	7 (64%)	0.03
Clinical re-event, n (%)	0 (0%)	5 (45%)	0.03
Restenosis, n (%)	1 (13%)	6 (55%)	0.068
Specific complications, n (%)	0 (0%)	2 (18%)	0.21
Generic complications, n (%)	0 (0%)	1 (9%)	0.39
Technical failure, n (%)	1 (13%)	0 (0%)	0.24
Number of devices used, median (IQR)	1 (1–2)	3 (2–4)	0.003

*Technical success; defined as <50% residual stenosis at the end of the intervention.
mRS, modified Rankin Scale.

Restenosis rate—defined as any radiological evidence of stenosis degree >50%—tended to be higher in Wingspan treated patients (n=6) than in the Elutax patients (n=1, P=0.068).

One death occurred owing to fatal vertebrobasilar stroke not related to the intervention (table 2).

Technical success—defined as <50% residual stenosis at the end of the interventional procedure—was achieved in 63% of the Elutax patients and 64% of the Wingspan patients (P=0.96). Furthermore, significantly fewer different devices were needed for successful recanalization in the Elutax group which required one device (median, IQR 1–2) for each case compared with three devices (median, IQR 2–4) for each case in the Wingspan group (P=0.003) (table 2).

There were no intraprocedural complications in 15/19 patients. Overall technical failure was 5% due to unsuccessful deployment of a pDEB because of difficult local anatomical conditions in an Elutax patient (Elutax: 13%; Wingspan: 0%, P=0.24). Generic complications were reported for only one Wingspan patients (9%) due to a groin hematoma at puncture site, which had to be surgically evacuated. Specific complications were seen in two Wingspan-treated patients: one had an intraprocedural in-stent thrombosis and the other had a consecutive hyperperfusion syndrome with transient neurological deterioration. No other procedure-related neurological complications, such as vessel perforation, dissections, subarachnoid hemorrhage, intracranial hemorrhage, or ischemic events, were found (table 2).

Finally, there were no differences between the two groups in good clinical outcome (modified Rankin Scale (mRS) score ≤2, (table 2), with a median mRS of 1 (IQR 0–3) for the Elutax patients, and a median mRS of 1 (IQR 0–2) for the Wingspan patients, respectively (P=0.95).

DISCUSSION

To our knowledge, this is the first cohort study reporting a pDEB specifically dedicated to neurovascular application (Elutax SV) and the Wingspan stent system in patients with intracranial symptomatic high-grade atherosclerotic arterial stenosis. During a median follow-up period of 9.5 months (Elutax) and 10 months (Wingspan), recurrent stroke/TIA was significantly lower in Elutax-treated patients than in the Wingspan group. Likewise, restenosis tended to be lower in Elutax patients. There was no significant difference in complication rate and outcome at follow-up.

ICAD is a common cause of ischemic stroke and patients with high-grade intracranial stenosis (70–99%), in particular, are at high risk of developing an ischemic event in the vascular territory of the stenosis.[17] These lesions may be amenable to intracranial angioplasty, but several concerns have been raised about this technique.

Evidence derived from cardiology has proved the efficacy and safety of DEB in coronary angioplasty. Since the first RCT of pDEB in coronary angioplasty for in-stent thrombosis, which found a significantly lower restenosis rate in the pDEB group (5% vs 43%, P=0.002),[9] the benefit of pDEB has become evident and the superiority of pDEB over conventional balloon catheters has also been proved in long-term follow-up studies.[18 19]

Conversely, the role of DEB, and especially pDEB, in the neurovascular setting is still unclear. Since the publication of the SAMMPRIS trial in 2011,[2] best medical care is regarded as the preferred treatment for ICAD because of the high periprocedural complication rate of 14.7%. This rate was considerably higher than in previously published data— for example, data from the European INTRASTENT multicentric registry, which had an intrahospital event rate of 7%.[20] Furthermore, a high incidence of recurrent stenosis of up to 31% appears to be a major problem with intracranial stenting, despite growing experience in procedural feasibility, safety, and durability of revascularization.[21 22] These restenoses may result in up to 39% of patients having a TIA or stroke.[23] Therefore, enthusiasm for using intracranial stenting has declined over the past years.

A review of intracranial angioplasty showed a relatively low incidence of 30-day major complications of ≤6%, but the rate of symptomatic and angiographic restenosis after 6 months was still 5–30%.[24] By using drug-eluted devices for the ICAD treatment, the rate of restenosis and clinical re-events may be reduced, as was shown in early studies.[11–13] However, their efficacy has not yet been totally confirmed in ICAD. So far, a study of a large cohort of 95 patients with ICAD treated with a sirolimus-coated coronary DES system (Coroflex Plaese Stent) has reported promising results, with a low restenosis rate of 3.9% and a low periprocedural complication rate of 0.9%.[10] In our study, a paclitaxel-coated balloon specifically designed for neurovascular application was used. Restenosis is mainly caused by intimal hyperplasia. Paclitaxel is a highly lipophilic anticancer drug and has an antiproliferative effect. By inhibiting the proliferation of smooth muscle cells, paclitaxel reduces intimal hyperplasia.[25] Thus, paclitaxel has been proved to be a potent agent to prevent restenosis.[26]

Preliminary good results with pDEB have been shown in different small case series for the treatment of restenosis in internal carotid artery stenosis.[27 28] But, experience of pDEB treatment in ICAD is limited to only one case series of 51 patients with ICAD, demonstrating a significantly lower restenosis rate than with a conventional stent system (9% vs 50%) during a mean follow-up of 6.5 and 7.5 months, respectively.[29] Our results support these findings that pDEB-treated patients have less restenosis and fewer cerebrovascular re-events than patients treated with conventional bare-metal stent and uncoated balloon catheters. The relatively high rate of restenosis of 36% in our Wingspan group is not surprising and is in-line with previous reports of up to 34%.[24]

Interestingly, despite the submaximal angioplasty technique with greater residual stenosis, the restenosis rate remained low. This is of special interest, because there are concerns about the effective interaction of the drug-coated surface of the DEB and the targeted vessel walls when the submaximal angioplasty technique is applied.[24]

Furthermore, the technical success rate was lower for both groups (Elutax vs Wingspan) with 63% and 64%, respectively, compared with previous studies with success rates of 70–100%.[22] Our results might be related to the submaximal angioplasty technique and low patient number. Despite the small number of patients, the technical failure rate was comparably low, with only one unsuccessful pDEB deployment in an anatomically difficult lesion. The deployment failure might be due to the greater rigidity and stiffness of the balloon because of the coated surface. Subsequent technical advances in catheter design may overcome this problem in the future, and may lead to softer and more flexible balloons.

No other severe incidents, such as vessel perforation, dissections, subarachnoid hemorrhage, or intracranial hemorrhage, occurred either in the short or long term. Therefore, the overall safety for the pDEB patients was good and lower as reported for PTAS patients in a recent meta-analysis.[30] Thus, a large sample size is needed, to definitively confirm the success rate and safety profile of the Neuro Elutax SV.

Finally, clinical outcome was favorable, with a median mRS score of 1 in both groups. However, there are differences in the initial NIHSS and clinical presentation in the two groups with insignificant, but a higher proportion of TIAs in the pDEB patients than in the PTAS patients, which might have biased the outcome for each group.

Major limitations are the retrospective design, lack of randomization and the small number of eligible patients because following the SAMMPRIS trial, patients with ICAD are primarily treated with platelet inhibitors without mechanical recanalization. Furthermore, the follow-up was relatively short. Because of the retrospective design, routine follow-up DSA to describe the treated stenosis at 90 days is not a common procedure at our institution, thus follow-up imaging is always based on ultrasound or other non-invasive imaging techniques. In addition, these data are obtained from only one experienced high-volume single center and thus may not be generally applicable.

Finally, our observations suggest that drug-eluting balloon angioplasty might be a valid option for patients with ICAD with intractable disease despite best medical care, because the technical advances of newer DEB generations has led to a lower complication rate with an overall good clinical and radiological outcome. Thus, large-scale, prospective studies are needed.

CONCLUSION

The pDEB Neuro Elutax SV may be a promising alternative treatment for highly selected patients with ICAD, showing a lower recurrence rate than with the PTAS Gateway/Wingspan with a similar safety profile and technical success rate. Despite a significant difference in the recurrence rate, conclusions have to be reached with caution owing to the limitations of this study. Further studies will be needed to clearly elucidate the role of pDEB in the management of symptomatic intracranial high-grade stenosis.

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