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Silent Embolic Infarction after Neuroform Atlas Stent-Assisted Coiling of Unruptured Intracranial Aneurysms

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Objective : There is still controversy regarding whether neck remodeling stent affects the occurrence of silent embolic infarction (SEI) after aneurysm coiling. Thus, the aim of the present study is to investigate the incidence of SEI after stent-assisted coiling (SAC) using Neuroform Atlas Stent (NAS) and possible risk factors. This study also includes a comparison with simple coiling group during the same period to estimate the impact of NAS on the occurrence of SEI.

Methods : This study included a total of 96 unruptured intracranial aneurysms in 96 patients treated with SAC using NAS. Correlations of demographic data, aneurysm characteristics, and angiographic parameters with properties of SEI were analyzed. The incidence and characteristics of SEI were investigated in 28 patients who underwent simple coiling during the same period, and the results were compared with the SAC group.

Results : In the diffusion-weighted imaging obtained on the 1st day after SAC, a total of 106 SEI lesions were observed in 48 (50%) of 96 patients. Of these 48 patients, 38 (79.2%) had 1–3 lesions. Of 106 lesions, 74 (69.8%) had a diameter less than 3 mm. SEI occurred more frequently in older patients (≥60 years, p=0.013). The volume of SEI was found to be significantly increased in older age (≥60 years, p=0.032), hypertension (p=0.036), and aneurysm size ≥5 mm (p=0.047). The incidence and mean volume of SEI in the SAC group (n=96) were similar to those of the simple coiling group (n=28) during the same period.

Conclusion : SEIs are common after NAS-assisted coiling. Their incidence in SAC was comparable to that in simple coiling. They occurred more frequently at an older age. Therefore, the use of NAS in the treatment of unruptured intracranial aneurysm does not seem to be associated with an increased risk of thromboembolic events if antiplatelet premedication has been performed well.

Key Words : Endovascular procedures · Coil · Stents · Diffusion magnetic resonance imaging · Embolic stroke · Intracranial aneurysm.

INTRODUCTION

Recently, Neuroform Atlas Stent (NAS) (Stryker Neurovascular, Kalamazoo, MI, USA) with low-profiled, easy handling deliveries is being widely applied for wide-necked intracranial aneurysms[14]. Although stent-assisted coiling (SAC) has been reported to be safe and effective in treating wide-necked aneurysms, this technique requires an adjunctive device (the

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stent) to be remained within the artery, which can increase the rate of periprocedural thromboembolic events. Generally believed to be caused by microemboli created during or after coil embolization, most thromboembolic events are clinically silent[2]. These lesions can be caused by various intra-procedural embolic sources including friable plaques, dissection of parent vessels, air bubbles, and thrombi within aneurysms and catheters that could only be detected by post-procedural diffusion weighted imaging (DWI)[20]. However, there is increasing evidence that the cumulative burden of ischemic brain injury might cause minor deficits or aggravate vascular dementia, especially in older patients with smaller brain volumes and decreased neuronal plasticity[24].

At a time when the use of NAS is increasing worldwide due to its convenience, the impact of NAS on the occurrence of silent embolic infarction (SEI) after aneurysm coiling remains unclear. Thus, the purpose of this study was to evaluate the incidence and risk factors for SEI after SAC, particularly the impact of NAS on the occurrence of SEI.

MATERIALS AND METHODS

The study was approved by the Research Ethics Board of Pusan National University Hospital (IRB number 2305-002-126).

Study population

Angiographic and clinical records were retrospectively analyzed in all patients who underwent NAS-assisted coiling for unruptured intracranial aneurysm (UIA) at Pusan National University Hospital between March 2018 and December 2022. Since January 2018, our institution has performed DWI on the first postoperative day for all patients who have undergone endovascular coiling for UIA regardless of the use of a stent. Other stents except NAS were excluded from this study. Dissecting or fusiform aneurysms, blood blister-like aneurysms, aneurysms associated with a brain arteriovenous malformation, and traumatic or mycotic aneurysms were also excluded. In addition, UIAs treated with more than two stents or patients treated for more than two aneurysms at the same time were excluded from this study. The presence of new focal diffusion abnormalities (areas of hyperintensity) on the postoperative DWI was regarded as a SEI. In addition, SEI did not cause symptoms and was confined to lesions that were found only in the territory of the endovascularly treated vessel. Clinical, angiographic, and procedure-related events related to the occurrence of SEIs in patients were analyzed. Medical data were collected prospectively in accordance with our protocol and reviewed retrospectively.

Procedure and analyses

All patients received a dual antiplatelet medication including 75 mg of clopidogrel (Plavix; Bristol-Myers Squibb, Washington, DC, USA and Sanofi Aventis, Bridgewater, NJ, USA) and 100 mg of acetylsalicylic acid for over 5 days or a loading dose of 300 mg of clopidogrel and 300 mg of acetylsalicylic acid at least 12 hours before the procedure. All procedures were performed by one experienced neuro interventionist (J.K.K.) were included in this study to reduce bias between treatment methods. All procedures were performed via a unilateral or bilateral transfemoral approach under intravenous sedation with full anticoagulation using intravenous heparin. Prior to the therapeutic procedure, patients were systemically administered heparin, in addition to a bolus injection of 3000 IU heparin. An additional bolus of 1000 IU heparin was administered every hour to maintain an activated coagulation time at 2–3 times the baseline throughout the procedure. An appropriate NAS size was selected (available diameters : 3.0–4.5 mm; available lengths : 15–21 mm) in such a way that the stent diameter was 0.5 mm larger than the parent vessel diameter and ends of the device would extend at least 5 mm beyond the neck of the aneurysm on each side. With regard to how to place the microcatheter tip into the aneurysm sac, we preferred the microcatheter jailing technique when performing the SAC procedure. Embolization was stopped when dense coil packing was obtained and no additional coil could be safely inserted. After the procedure, 100 mg acetylsalicylic acid and 75 mg clopidogrel were administered daily. Acetylsalicylic acid and clopidogrel resistance test were performed using a VerifyNow P2Y12 assay (Accumetrics, Inc., San Diego, CA, USA) shortly after the procedure. In patients who were poor responders to clopidogrel, cilostazol was administrated. After coil embolization, patients routinely underwent DWI within 24 hours post-procedure as a protocol for detecting procedure-related ischemic complications. Imaging was performed using a 1.5 or 3 Tesla MRI (magnetic resonance imaging) system (Signa HDxt 1.5T, Signa Excite HDx 3.0T; GE

Healthcare, Chicago, IL, USA). If DWI abnormalities were detected, their numbers, locations, and sizes were recorded. Whole ischemic volume in each patient was calculated with the following formula : V=3.14×a×b×4.

In the formula, a and b were major and minor axes of the ellipse, respectively. We assumed that the ischemic lesion was a column with an ellipse at its base. We then obtained the ischemic volume by adding the sum of volumes of each column. For this study, we found only the embolic type of new ischemic lesions. These lesions were found only in the territory of the endovascularly treated vessel. Images from head MRI were interpreted by two experienced neuroradiologists (T.H.L. and L.H.). Disagreements between these neuroradiologists were resolved by consensus reviews.

This retrospective study examined the variables associated with SEI. Clinical, aneurysmal, and procedural factors were recorded and analyzed. These factors were as follows : age, sex, history of cigarette smoking, hypertension, diabetes mellitus, dyslipidemia, previous ischemic comorbidity, aneurysm size (maximum size), location, stent length, and procedure time. Additionally, we compared our results of SAC with those ofa simple coiling group during the same period to estimate the impact of NAS on the occurrence of SEI.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics version 27 (IBM Corp, Armonk, NY, USA). Continuous variables are expressed as mean±standard deviation. The significance of differences between two groups was examined using Student's t-test and Mann-Whitney test for continuous variables or chi square and Fisher's exact test for categorical variables. A *p*-value of less than 0.05 for a 95% confidence interval (CI) was considered to be statistically significant.

RESULTS

SEI of the SAC group

A total of 96 aneurysms in 96 patients were included in this study (77.1% women, 22.9% men; mean age, 63.4±10.3 years). Characteristics of the study cohort are presented in Table 1. Most aneurysms (86.5%) were located in the anterior circulation, and the internal carotid artery was the most frequent location (56.2%). An aneurysm over 5 mm accounted for 55.2%, and the most frequently used stent was 4.5/21 mm (59.4%). Overall, 106 SEI lesions were observed in 48 (50%) of 96 patients. Of these 48 patients, 38 (79.2%) had 1–3 lesions and 10

Table 1. Patient demographic data and aneurysm characteristics in SAC group (n=96)

Characteristic	Value
Sex	
Male	22 (22.9)
Female	74 (77.1)
Age	
<60 years	30 (31.1)
≥60 years	66 (68.9)
Aneurysm location	
Internal carotid artery	54 (56.2)
Anterior communicating artery	14 (14.6)
Anterior cerebral artery	4 (4.2)
Middle cerebral artery	2 (2.1)
Posterior communicating artery	9 (9.4)
Basilar/vertebral artery	10 (10.4)
Superior cerebellar artery	2 (2.1)
Posterior cerebral artery	1 (1.0)
Aneurysm diameter	
<5 mm	43 (44.8)
≥5 mm	53 (55.2)
Stent size	
4.5/21 mm	57 (59.4)
4.0/21 mm	11 (11.4)
3.0/21 mm	5 (5.2)
3.0/15 mm	23 (24.0)

Values are presented as number (%). SAC : stent-assisted coiling

Table 2. Characterization of SEI lesions observed in SAC group and simple coiling group

	SAC group (n=106)	Simple coiling group (n=34)
Diameter of ischemic lesion		
<3 mm	74 (69.8)	25 (73.5)
3–6 mm	27 (25.5)	8 (23.5)
>6 mm	5 (4.7)	1 (3.0)
Volume of ischemic lesions (mm^3)	31.83±47.40	34.20±59.59

Values are presented as mean±standard deviation or number (%). SEI : silent embolic infarction, SAC : stent-assisted coiling patients (20.8%) had ≥4 lesions. Among 106 lesions, 74 lesions (69.8%) were <3 mm in diameter; 27 lesions (25.5%) had a diameter between 3 and 6 mm, and five lesions (4.7%) had a diameter >6 mm (Table 2). Fortunately, no symptomatic hemorrhage or infarction occurred in all patients. Patient and aneurysm characteristics according to the appearance of SEI lesions are shown in Table 3. Only older age (≥60 years) was significantly associated with SEI lesions (p=0.013). No significant association was found with respect to sex, diabetes mellitus, hypertension, dyslipidemia, ischemic heart disease, stent length, or procedure time. To compare volumes of SEI lesions between patients, the total volume of SEI lesions was determined (Table 4). The volume of SEI lesions was found to be significantly increased in older age (≥60 years, p=0.032), hypertension (p=0.036), and aneurysm size (≥5 mm, p=0.047). Procedure time and pre-interventional plavix reaction unit value had no significant effect on SEI volume.

Table 3. Patient and aneurysm characteristics according to appearance of SEI lesions

	SEI lesion		p-value
	No	Yes	
Sex			0.331
Male	13 (59.1)	9 (40.9)	
Female	35 (47.3)	39 (52.7)	
Age			0.008
<60 years	21 (70.0)	9 (30.0)	
≥60 years	27 (40.9)	39 (59.1)	
Diabetes mellitus			0.199
Yes	3 (27.3)	8 (72.7)	
No	45 (52.9)	40 (47.1)	
Hypertension			0.682
Yes	21 (47.7)	23 (52.3)	
No	27 (51.9)	25 (48.1)	
Dyslipidemia			0.662
Yes	16 (53.3)	14 (46.7)	
No	32 (48.5)	34 (51.5)	
Ischemic heart disease			0.111
Yes	1 (14.3)	6 (85.7)	
No	47 (52.8)	42 (47.2)	
Smoking			0.053
Yes	12 (75.0)	4 (25.0)	
No	36 (45.0)	44 (55.0)	
Aneurysm size			0.538
<5 mm	23 (53.5)	20 (46.5)	
≥5 mm	25 (47.2)	28 (52.8)	
Stent length			0.473
15 mm	10 (43.5)	13 (56.5)	
21 mm	38 (52.1)	35 (47.9)	
Procedure time			0.533
<50 minutes	30 (52.6)	27 (47.4)	
≥50 minutes	18 (46.2)	21 (53.8)	

Values are presented as number (%). SEI : silent embolic infarction

SEI of the simple coiling group

In the simple coiling group, 34 SEI lesions were detected in 16 (57.1%) of 28 patients. Among 34 lesions, 25 lesions (73.5%) were <3 mm in diameter; eight lesions (23.5%) had a diameter between 3 and 6 mm, and one lesion (2.9%) had a diameter >6 mm (Table 2). Like the SAC group, there was no ischemic lesion that caused neurologic symptom in the simple coiling group. The incidence and characteristics of SEI lesions in the simple coiling group were similar to those in the SAC group. Mean volumes of SEI lesions in the simple coiling group and the SAC groups were 34.20±59.59 mm^3 and 31.83±47.40 mm^3, respectively, showing no significant difference between the

Table 4. The correlation between risk factors and ischemic volume in the SAC group

	Ischemic volume (mm^3)	p-value
Age		0.032
<60 years	16.54	
≥60 years	38.77	
Hypertension		0.036
Yes	42.82	
No	22.52	
Aneurysm size		0.047
<5 mm	32.68	
≥5 mm	55.43	
Procedure time		0.231
<50 minutes	26.83	
≥50 minutes	39.13	
Clopidogrel		0.914
<208 PRU	32.32	
≥208 PRU	31.26	

SAC : stent-assisted coiling, PRU : plavix reaction unit two (p=0.637, Table 2).

DISCUSSION

This study investigated the incidence and characteristics of SEI after NAS-assisted coiling for the treatment of UIAs and analyzed several risk factors according to the presence of SEI. The major finding of the study was that SEI lesions were observed in 48 (50%) of total 96 patients and among them, those who had 1–3 lesions accounted for 79.2%. In addition, 69.8% of SEI lesions were <3 mm in diameter. Fortunately, there were no SEI associated with symptom. Older age (≥60 years) was significantly associated with the occurrence of SEI. The volume of SEI lesions was found to be significantly increased in older age (≥60 years), hypertension, and larger aneurysm size (≥5 mm). Furthermore, when comparing the SAC group and the simple coiling group done during the same period, there was no significant difference in the incidence or mean volume of SEI.

NAS can be delivered via a 0.0165- or a 0.017-inch microcatheter such as an Excelsior SL-10 (Stryker Neurovascular), one of the most widely used microcatheters for coil embolization[8,14]. The cell size of the NAS is small compared to that of its old version, which allows better coil retention in aneurysms. However, SAC requires that a foreign body (the stent) remain within the artery, which can increase the risk of procedure-related thromboembolic complications. Most reports on the NAS have concluded that NAS-assisted coil embolization is safe and effective in treating wide-necked aneurysms[10,16,25]. Recently, Kwon and Chung[14] have reported outcomes of SAC using NAS in 123 patients with 130 unruptured wide-necked aneurysms. The authors reported a procedure-related complication rate of 6.2%, including 3.8% of thromboembolism, which had no symptoms. Burkhardt et al.[3] have reported that the incidence of symptomatic thromboembolism in 128 patients with 128 aneurysms treated with NAS-assisted coiling is 4.7%. Despite the explosive increase in global use of this smallest profiled NAS, there has been few reports on SEI after NAS-assisted coiling to the best of our knowledge. Furthermore, according to a recent meta-analysis on the association between SEIs and cognitive function, SEI might be a factor inducing cognitive dysfunction[17]. Therefore, SEI has clinical significance because it can lead to a decline in cognitive function and increase the risk of dementia in the long term[17,24].

Among studies on SEI after aneurysm coiling, there are many studies related to incidence and risk factors. However, few studies have examined characteristics of ischemic lesions. Hahnemann et al.[7] have reported a silent embolism after SAC in their 75 consecutive cases, regardless of the type of stent. Silent embolisms were observed relatively high at 64% in their 75 consecutive patients. 70.1% of silent embolisms had 1–3 ischemic lesions and most (87.1%) of the ischemic lesions were <5 mm in diameter. These characteristics of SEI are very similar to results of our study.

Numerous studies have already investigated postprocedural DWI-positive lesions in endovascular coiling for cerebral aneurysms[1,2,11,12,19]. These lesions can be produced by manipulating the guiding catheter, difficulty of aneurysm selection, event during framing coil, amounts of coils, detachment method, surgeon's experience, and perioperative antithrombotic agent. In these studies, detection rate is reported very widely at around 10–70%. This variability of incidence can be attributed to reasons such as differences in scan settings of MRI systems, medical conditions of patient, and premedication for periprocedural thromboembolism. The incidence of SEI (50%) in the present study was within the aforementioned range.

Regarding conditions affecting the occurrence of SEI, many studies have shown positive associations between various factors (including older age, dyslipidemia, diabetes mellitus, previous ischemic stroke, presence of white matter lesions, ruptured aneurysms, multiple aneurysms, larger dome size, larger neck size, and longer procedural time) and postprocedural DWI-positive lesions[1,9,13,19,23]. In the present study, older age, hypertension, and larger dome size were positively associated with postprocedural SEI volume, similar to previous reports. Increasing age might be related to tortuous large vessels including aortic arch, brachiocephalic trunk, common and internal carotid arteries, and tortuous origin of the vertebral artery. Catheterizing tortuous arteries could increase the risk of thromboembolism. Seo et al.[22] have reported that the occurrence of SEI increases at an older age of >55 years. The authors assumed that more atherosclerotic changes in the cerebral artery were present in older patients and that these patients were more vulnerable to thromboembolic events. High blood pressure is also well known as an important cause of atherosclerotic change in cerebral blood vessels. It can be easily explained as a risk factor in SEI. Several papers have already demonstrated that larger aneurysms are associated with increased risk of periprocedural ischemic stroke[6,23,26]. Intra-aneurysmal clot is more frequent in larger aneurysms before endovascular treatment and larger aneurysms are more likely to have residual flow within the coil mass than small aneurysms. Furthermore, for stent deployment, large size aneurysms can make it difficult to achieve good wall apposition, thus increasing the risk of periprocedural ischemic stroke. The present study also found that aneurysm size (≥5 mm) was significant risk factor for the occurrence of SEI after NAS-assisted aneurysm coiling. Regarding other risk factors, there are several reports that have proved a close correlation between procedure time and the occurrence of SEI, although not demonstrated in the present study[7,15]. Lee et al.[15] have reported that every 10 minutes increase in the procedure time was independently associated with the risk of thromboembolism, after adjusting the analysis (adjusted odds ratio, 1.11; 95% CI, 1.01–1.21). According to report on SEI after SAC of UIAs studied by Hahnemann et al.[7], the number of patients with DWI lesions was significantly increased in older patients (≥55 years) and longer intervention times (≥120 minutes). In addition, with the recent increase in the application of flow diverter to the treatment of UIAs, flow diverter is also emerging as an important risk factor for the occurrence of SEI[26].

Whether neck remodeling stent increases postprocedural SEI lesions in endovascular treatment for cerebral aneurysm remains controversial. Several studies have demonstrated positive associations between SAC and postprocedural DWI-positive lesions, whereas others have not[5,7,19]. Schubert et al.[21] have compared the rate of embolic events in patients treated with SAC with that in those treated with coiling alone. The authors observed no significant difference in rate of embolic events between the two procedures. In the present study, we observed DWI lesions in 50% of all SAC cases (n=96) and 57.1% of all simple coiling group (n=28). In the group without NAS, the incidence of SEI was rather slightly higher. Although accurate comparisons might be difficult due to the small number of controls, the authors carefully agree that NAS with low profiled has a minimal impact on the occurrence of SEI. This is a surprising result since SAC involves increased technical complexity.

To our best knowledge, there are few studies on the difference in thrombosis incidence according to the type of stent. Nii et al.[18] evaluated the incidence and timed the development of acute in-stent thrombosis during SAC with braided- or laser-cut stents. The authors reported that there was no significant difference in the incidence of in-stent thrombosis between the different stent types and it developed earlier after the placement of braided stents. They suggested lower wall shear stress due to denser metal coverage of braided stents as the reason why thrombus formation occurs earlier in braided than laser-cut stents[4,18].

The present study had several limitations including its retrospective data collection and a small number of control group treated with simple coiling. Thus, effects of possible selection bias cannot be excluded. Another limitation of this study was the lack of acquisition of a pretreatment DWI sequence. Thus, we cannot completely eliminate the possibility that some of the DWI lesions might have been due to other causes including pre-procedural diagnostic angiography. NAS-coil embolization was performed after approximately 2 weeks diagnostic angiography. Therefore, we tried our best to distinguish between previous and new DWI positive lesions through differences in signal intensity. Moreover, owing to a single-center design, the present results might be specific to our techniques and machines. Finally, two different MRI systems were used for assessing the appearance of DWI-positive lesions.

CONCLUSION

A total of 106 SEI lesions were observed in 48 (50%) of 96 patients. SEI occurred more frequently in older patients and the volume of SEI was found to be significantly increased in older age (≥60 years), hypertension, and aneurysm size ≥5 mm. SEIs are common after NAS-assisted coiling with an incidence comparable to those after simple coiling. Most SEIs were less than 3 mm in diameter and consisted of 1–3 lesions. SEI rarely caused symptoms as expected. They occurred more frequently at an older age. Therefore, the authors agree that the use of NAS in the treatment of UIA does not seem to be associated with an increased risk of thromboembolic events if antiplatelet premedication has been performed well. Further studies should focus on the relationship between SEIs and their long-term clinical effects.

AUTHORS' DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : SS, JKK; Data curation : SS; Formal analysis : SS; Methodology : SS, JKK; Project administration : JKK; Visualization : SS, LH, THL; Writing - original draft : SS, JKK; Writing - review & editing : LH, THL

Data sharing

None

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