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Clinical Article

In-Stent Stenosis of Stent Assisted Endovascular Treatment on Intracranial Complex Aneurysms

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Objective : To introduce the frequency and segment analysis of in-stent stenosis for intracranial stent assisted endovascular treatment on complex aneurysms.
Methods : A retrospective study was performed in 158 patients who had intracranial complex aneurysms and were treated by endovascular stent application with or without coil embolization. Of these, 102 patients were evaluated with catheter based angiography after 6, 12, and 18 months. Aneurysm location, using stent, time to stenosis, stenosis rate and narrowing segment were analyzed.
Results : Among follow-up cerebral angiography done in 102 patients, 8 patients (7.8%) were shown an in-stent stenosis. Two patients have unruptured aneurysm and six patients have ruptured one. Number of Neuroform stents were 7 cases (7.5%) and Enterprise stent in 1 case (11.1%). Six patients demonstrated in-stent stenosis at 6 months after stent application and remaining two patients were shown at 12 months, 18 months, respectively.
Conclusion : In-stent stenosis can be confronted after intracranial stent deployment. In our study, no patient showed symptomatic stenosis and there were no patients who required to further treatment except continuing antiplatets medication. In-stent stenosis has been known to be very few when they are placed into the non-pathologic parent artery during the complex aneurysm treatment, but the authors found that it was apt to happen on follow up angiography. Although the related symptom was not seen in our cases, the luminal narrowing at the stented area may result the untoward hemodynamic event in the specific condition.

KEY WORDS : Intracranial complex aneurysm · In-stent stenosis.

INTRODUCTION

The intracranial stent has been applied frequently and makes the complex aneurysm treatment possible with endovascular way. Before the device of self expandable intracranial stent like Neuroform (Boston Scientific/Target, Fremont, CA, USA) and Enterprise (Cordis Neurovascular, Miami Lakes, FL, USA) which have been available in Korea, coronary stents were used for the treatment of intracranial complex aneurysms. However, their rigidity made a difficult navigation through intracranial vessel and the excessive radial force on the parent artery lumen sometimes brought about very severe complications like early vasospasm, vessel injury and delayed in-stent stenosis with neointimal hyperplasia[4].

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In-stent stenosis after treatment of intravascular atheromatous disease in coronary artery is a relatively common complication and has incidence of between 10-50%[11]. And the risk of ischemic stroke due to stenosis in patients with intracranial atherosclerotic disease ranges from 8-22%[2,16].

Stent-assisted endovascular embolization of intracranial aneurysm was first reported by Higashida et al.[5] several years ago and it was admitted as a relative new idea in endovascular treatment. When this technique was introduced, the utility of technique was restricted by the technical limitation and commercial availability.

The neointimal hyperplasia rarely develops during deployment of stent which provides low radial force such as Neuroform or Enterprise. However, it has been more frequently reported with in-stent stenosis by neointimal hyperplasia as time has been passed since first application and increasing of follow-up patients. Some adverse effects such as in-stent stenosis have become known after aneurysm treatment using intracranial stent. The endothelialization and intimal growth over the stent are important factors of in-stent stenosis.

Additionally, neointimal hyperplasia has a crucial role of stenosis over stent segment that result in a hemodynamic remodeling of parent vessel[3]. Also, the self expanding intracranial stent has a very low intrinsic radial force, so trauma on parent vessel rarely occurs during procedure.

MATERTIALS AND METHODS

Patient data

Our center started to use intracranial stents as a treatment of intracranial aneurysm in October 2003. Since year 2003, a total of 158 patients have treated by stent assisted endovascular coil embolization and 102 patients have underwent stent assisted coil embolization for intracranial aneurysm and followed up in single center. All clinical records and radiologic findings were reviewed by two neurosurgeons. Of 102 patients, 93 patients were treated using Neuroform stent and 33 patients were treated using Enterprise stent.

Endovascular stent deployment technique

All procedures were performed under propofol sedation. All patients were fully heparinized targeting activated coagulation time of 250-300 seconds by intravenous heparin during procedure. Access was obtained through the right common femoral artery. We used 90 cm angled 6 Fr Envoy guiding catheter (Cordis Neurovascular, Miami Lakes, FL, USA) via right femoral artery access and SL-10 microcatheter (Target Therapeutics, Fremont, CA, USA) with 0.014 inch microguidewire. After the placement of a SL-10 microcatheter at distal target lesion on parent vessels, stent delivery system was advanced and positioned over across the aneurysm neck, and deployed. Secondly, coil embolization for aneurysm was performed with Guglielmi detachable coils, Matrix coils (Boston Scientific) and Microplex coils (Hypersoft, Microvention). Because the systemic heparinization and continuing antiplatelets medication has been kept, we mostly used closing device like Angioseal (St. Jude Medical, St. Paul, MN, USA) and Perclose (Abbott Laboratories. Abbott Park, IL, USA) to close the femoral puncture site. Most of patients were pretreated with dual anticoagulation (aspirin and clopidogrel) and were discharged on both aspirin (100 mg daily) and clopidogrel (75 mg daily). In our institution, patients take aspirin and clopidogrel for initial 3 weeks and after that, stop clopidogrel and continue aspirin. In the SPARCL (A secondary analysis of the stroke prevention by aggressive reduction in cholesterol levels), statin line drugs showed a 33% reduction in the risk of any stroke[14]. So our center recommend simvastatin (20 mg daily) to patients who have hyperlipidemia or coronary artery problems. However, some of patients missed initial follow-up and stopped voluntarily dual anticoagulation treatment.

Follow-up angiography

All follow-up conventional cerebral angiography was performed between 6 months and 3 years after initial stent deployment. Minimal diameter was measured and calculated to stenosis rate comparing previous cerebral angiography. We used same working view angle to reduce error. Stenosis was measured based on digital subtraction angiography by PACS (Picture Archiving Communication System).

We defined the stenosis as change of diameter comparing with previous angiography in parent vessel. We measured a diameter and calculated percentage of narrowing then excluded value below 20% because of bias on measurement.

We used stenosis segment analysis suggested by Daniel A. et al.[7]. We modified segment length and points were defined along the path of the parent artery; 1) 5 mm proximal to the stent (a), 2) 5 mm distal to the proximal struts (b), 3) segment at the aneurysm neck (c), 4) 5 mm proximal to the distal struts (d), and 5) 5 mm distal to the distal struts (e).

RESULTS

Patient population

A total of 158 patients were treated using stent for intracranial aneurysm and 170 stents were used between October 2003 and March 2010 at our center. Of 170 stents (lesions), number of Neuroform stent was 137 (80.6%) and Enterprise stent 33 (19.4%). One-hundred-two patients (65.6%) in 158 patients have had follow-up conventional cerebral angiography evaluations. Of 102 cases with follow-up angiography, patients who used Neuroform stent were 93 in number and Enterprise stent in 9 cases. In this population, eight patients (stenosis rate; 7.8%) have demonstrated in-stent stenosis on follow-up cerebral angiography, including 2 patients unruptured aneurysm. Respectively, Neuroform showed 7.5% of stenosis rate and Enterprise showed 11.1% of stenosis rate. Age range of 8 patients was from 46 to 67 (mean age; 56) and ratio of sex was 1 : 1 (female n = 4 , male n = 4) (Table 1).

Clinical outcome

There was no clinical symptom associated with in-stent stenosis in any of 8 patients. We have prescribed dual antiplatelets therapy for all patients who underwent stent assisted coil embolizations unless patient had a contraindication for antiplatetlet drug. Six of 8 patients who demonstrated the in-stent stenosis had taken dual antiplatelets drug since endovascular procedure. Remaining 2 patients had a contraindication for antiplatelets agent (Table 2). Since year 2009, our institution started a statin-line drug for patients who under-

went stent associated procedure based on recent recommendation for in-stent stenosis.

Angiographic analysis

The locations of the aneurysm were basilar top (n = 2), posterior communicating artery (n = 4), anterior communicating artery (n = 1) and bifurcation of middle cerebral artery (n = 1). Six patients presented ruptured aneurysm and two patients presented unruptured aneurysm. Stenosis rate was measured on digital subtraction angiography and ranged from 20 to 90% (mean rate : 42.75%).

Case 7 had ≥ 90% stenosis at 6 months, Case 4 had 40% stenosis at 12 months, Case 3 had 37% stenosis at 18 months, and remaining patients showed ≤ 50% at 6 months (Table 2). None of these patients were symptomatic and did not require treatment for stenosis.

Angiographic follow-up

We demonstrated follow-up conventional angiography every 6 months from initial endovascular treatment. Five patients showed in-stent stenosis at first follow-up angiography. The other two patients showed in-stent stenosis at 12 months and 18 months, respectively. One patient showed stenosis on immediate postoperative angiography.

Spontaneous resolution of stenosis was found in only one patient of 8 patients at 6 months follow-up angiography from the time found in-stent stenosis.

Case illustrations

Case 1

A 47-year-old male patient (No. 7) was transferred from an outside hospital for evaluation of sudden onset headache. He complained intolerable headache and nausea. He had no specific medical history except smoking 1 pack per day for 2 decades. Initial GCS was E3M6V5 and Hunt-Hess grade was 2. Brain computed tomography at emergency room was done and revealed a spontaneous subarachnoid hemorrhage. We performed a diagnostic cerebral angiography and it showed two aneurysms at posterior communicating artery level on right side ICA. First, we deployed a stent from right ICA to M1 segment using a Enterprise (4.5 mm × 22 mm) stent. After that, we packed two aneurysms using Guglielmi detachable coils, Matrix coils (Boston Scientific) and Microplex coils (Hypersoft, Microvention). There were no perioperative complications and patient was treated in intensive care unit for 2 weeks and transferred to general ward. He was discharged without neurologic deficit. After 6 months, we performed a follow-up cerebral angiography and found a stenosis at end of stent (segment e). A stenosis rate was measured approximately more than 90% (Fig. 1).

Case 2

A 63-year-old male patient (No. 8) was referred for endovascular treatment. He had dizziness for several months. Brain magnetic resonance angiography done at previous hospital revealed an unruptured large aneurysm with broad neck. Conventional angiogram done at our institution showed a large aneurysm at right middle cerebral bifurcation. Aneurysm had a broad neck (5.9 mm) and we planned to perform 'Y-configuration' technique. We deployed two Neuroform (3.5 mm × 20 mm) stents from M1 segment to both M2 branches and packed aneurysm with Guglielmi

Table 1. Overall rates of in-stent stenosis

Total No. of patients	158
Total No. of stents (lesions)	170
Neuroform	137
Enterprise	33
Follow-up angiography	102
Neuroform	93
Stenosis	7 (7.5%)
Enterprise	9
Stenosis	1 (11.1%)
Total stenosis rate	8 (7.8%)

Table 2. Summary of 8 patients with in-stent stenosis.

Patient No.	Age (yr)/Sex	Aneurysm location	Rupture/ Unrupture	Stent type	Time to stenosis (mo)	Stenosis rate (%)	Segment analysis†	Medication
1	58/F	BT	R	N	6	20	b	A
2	56/F	BT	R	N	6	45	b	C
3	58/M	Lt. PcoA	UR	N	18	37	e	A + C
4	67//F	Rt. PcoA	R	N	12	40	c	None
5	51/F	Rt. PcoA	R	N	0*	40	e	None
6	49/M	AcoA	R	N	6	50	b	A + C
7	46/M	Rt. PcoA	R	E	6	90	d	A + C
8	63/M	Rt. MCA	UR	N	6	20	b	A + C

*The patient showed stenosis on immediately post operative angiography, †See the text in the section of Material and Methods (follow-up angiography : segment analysis). No. : number, BT : basilar top, PcoA : posterior communicating artery, AcoA : anterior communicating artery, MCA : middle cerebral artery, R : ruptured, UN : unruptured, N : Neuroform, E : Enterprise, A : aspirin only, C : clopidogrel only, A + C : aspirin and clopidogrel

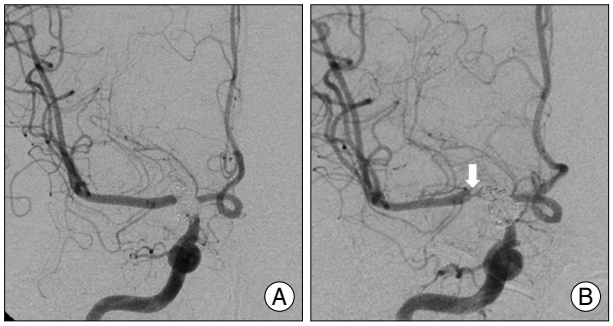

Fig. 1. A : Right internal carotid artery angiography demonstrates complete occlusion in two posterior communicating artery aneurysms. B : After 6 months, follow-up cerebral angiography shows a stenotic change (white arrow) at M1 segment which is just end of a stent placement.

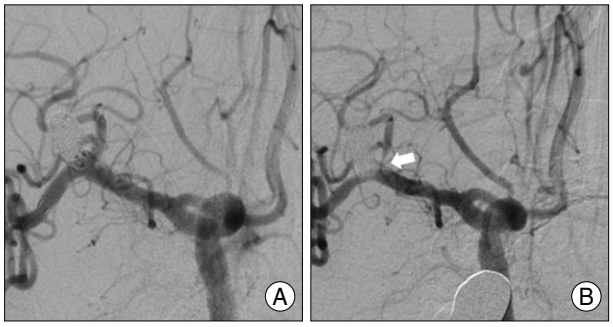

Fig. 2. A : Immediate post operative angiography shows coil loop protrude into parent artery and 'Y-configuration' stents deployment. B : In-stent stenosis at one of M2 branch is shown (white arrow) in 6 months follow-up cerebral angiography and protruded coil is compacted comparing immediate post operative angiography.

detachable coils, the Matrix coils and Microplex coils.

He was discharged without any symptoms and had follow-up cerebral angiography after 6 months. There was an in-stent stenosis at one of the M2 branch (segment d) (Fig. 2).

DISCUSSION

Intracranial stent is a highly versatile device for the treatment of intracranial aneurysm but as a novel device, relatively little is understood regarding the long-term significance of its use[3]. Before introduction of self-expanding intracranial stent, coronary stents were used and there was limitation for application in treatment of cerebral aneurysm. The coronary stents were insufficient due to their inflexibility. The tortuous parent vessels were often exposed a risk of dissection or rupture during stent navigation[10]. A brand-new intracranial stent (e.g., Neuroform stent) provide us much easier approach through tortuous intracranial parent artery because it had more flexible characteristics.

There is a proliferation and activation of regional smooth muscle cells, resulting in neointimal tissue formation, which can cause a restenosis within the stent[9]. Endothelial cells play a crucial role in the regulation of smooth muscle growth, and when regulation is ruined, neointimal proliferation results in stenosis[17]. In-stent stenosis is classically confronted within 3-6 months after treatment using intracranial stent[4,12]. Several histologic reports have shown a neointimal hyperplasia that represents the primary pathologic mechanism in in-stent stenosis[6,8].

Angioplasty balloon and intravascular stent cause endothelial injury which is implicated with degree of neointimal hyperplasia. Neointimal hyperplasia is histologically marked by proliferation of smooth muscle cell and immoderate production of extracellular matrix[4]. To our knowledge, only very few reports have studied the restenosis after the deployment of stents within the cerebral vessel for atheromatous disease.

Stenting of Symptomatic Atherosclerotic Lesions in the Veterbral or Intracranial Arteries (SSYLVIA) trial demonstrated that greater than 50% delayed in-stent narrowing was found in 32% of intracranial lesions and in 43% of extracranial lesions treated with balloon mounted Neurolink stent[15].

A fairly small number of endothelial disruption would be expected after the deployment of a self expanding stent which provide a very low radial force, consequently, the rate of in-stent stenosis would be expected to be much lower[3]. Moderate to severe in-stent stenosis with Neuroform self-expanding stent has been reported with an incidence of 5.8%[3]. Bose et al.[1] reported a rate of in-stent stenosis of 7.5% after 6 months. Levy et al. reported on the treatment for symptomatic intracranial atheromatous disease and showed a rate of in-stent stenosis of 29.7% and 4.8% of in-stent stenosis after mean time of 5.9 months[3]. Similarly, our results show an incidence of in-stent stenosis of 7.8% using Neuroform and Enterprise stents.

Symptomatic stenosis may occur in large study group. Fiorella et al.[3] reported symptomatic stenosis rate of 1.3%. Although the stenosis was asymptomatic in most cases, high grade, long segment, or tandem lesions were found in patients with symptomatic stenosis. In our study, fortunately, there was no case of symptomatic stenosis.

The resolution of in-stent stenosis can be observed on follow-up conventional angiography. This spontaneous resolution was first described by Fiorella et al.[3] and they commented this fact had an important clinical meaning for patients treatment, such as continuation of dual antiplatelet medication, close observation for neurological symptom, and follow-up angiography. Schatz et al.[13] reported in a animal model that the in-stent neointima became thick and nontransparent in the early phase, but became thinner and sclerotic in the later phase, with cell number decrease. One patients in our cases showed a spontaneous resolution of stenosis after 6 months from initial stenosis was observed. In our study, only

one patient showed a spontaneous resolution of stenosis and we established own protocol for in-stent stenosis as following : 1) strict medication schedule (dual antiplatelets plus HMA-CoA reductase inhibitor), 2) follow-up cerebral angiography every 6 months, 3) educate patient to visit hospital without delay in case of any neurologic change, and 4) regular monitoring of hyperlipidemia.

There are limitations to this study being a retrospective nature, small number of cases and short follow up period. The long-term follow-up is necessary in future study to settle the in-stent stenosis rate for intracranial stent application. Also, a large series of in-stent stenosis cases will be necessary to establish a statistic analysis such as the frequent involved location and relationship between aneurysm characteristics and in-stent stenosis.

CONCLUSION

In-stent stenosis after endovascular intracranial aneurysm treatment by using self expanding stents occurred in up to 7.8% in our study indicating that it has a latent possibility of delayed in-stent stenosis as a complication of stent assisted endovascular coil embolization. Symptomatic stenosis did not occur in our study group, however it can be changed into symptomatic stenosis depending on stenosis rate, and length of stenosis lesion.

References

1. Bose A, Hartmann M, Henkes H, Liu HM, Teng MM, Szikora I, et al. : A novel, self-expanding, nitinol stent in medically refractory intracranial atherosclerotic stenoses : the Wingspan study. **Stroke 38** : 1531-1537, 2007
2. Chimowitz M, Lynn M, Howlett-Smith H, Stern B, Hertzberg V, Frankel M, et al. : Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. **N Engl J Med 352** : 1305-1316, 2005
3. Fiorella D, Albuquerque F, Deshmukh V, McDougall C. : In-stent stenosis as a delayed complication of Neuroform stent-supported coil embolization of an incidental carotid terminus aneurysm. **AJNR Am J Neuroradiol 25** : 1764-1767, 2004
4. Fiorella D, Albuquerque F, Woo H, Rasmussen P, Masaryk T, McDougall C : Neuroform in-stent stenosis : incidenace, natural history, and treatment strategies. **Neurosurgery 59** : 34-42, 2006
5. Higashida R, Smith W, Gress D, Urwin R, Dowd C, Balousek P, et al. : Intravascular stent and endovascular coil placement for a ruptured fusiform aneurysm of the basilar artery. Case report and review of the literature. **J Neurosurg 87** : 944-949, 1997
6. Hoffmann R, Mintz G, Dussaillant G, Popma J, Pichard A, Satler L, et al. : Patterns and mechanisms of in-stent restenosis: a serial intravascular ultrasound study. **Circulation 94** : 1247-1254, 1996
7. Hoit D, Malek A : Three-dimensional rotational angiographic detection of in-stent stenosis in wide-necked aneurysm treated with a self-expanding intracranial stent. **Neurosurgery 57** : 1228-1236, 2005
8. Kearney M, Pieczek A, Haley L, Losordo D, Andres V, Schainfeld R, et al. : Histopathology of in-stent restenosis in patients with peripheral artery disease. **Circulation 95** : 1998-2002, 1997
9. Kipshidze N, Dangas G, Tsapenko M, Moses J, Leon M, Kutryk M, et al. : Role of the endothelium in modulating neointimal formation : Vasculoprotective approaches to attenuate restenosis after percutaneous coronary interventions. **J Am Coll Cardiol 44** : 733-739, 2004
10. Layton K, Hise J, Thacker I : Recurrent intracranial stenosis induced by the Wingspan stent: comparison with balloon angioplasty alone in a single patient. **AJNR Am J Neuroradiol 29** : 1050-1052, 2008
11. Lowe H, Oesterle S, Khachigian L : Coronary in-stent restenosis : current status and future strategies. **J Am Coll Cardiol 39** : 183-193, 2002
12. Marks M, Wojak J, Al-Ali F, Jayaraman M, Marcellus M, Connors J, et al. : Angioplasty for symptomatic intracranial stenosis : clinical outcome. **Stroke 37** : 1016-1020, 2006
13. Schatz R, Palmaz J, Tio F, Garcia F, Garcia O, Reuter S : Balloonexpandable intracoronary stents in the adult dog. **Circulation 76** : 450-457, 1987
14. Sillesen H, Amarenco P, Hennerici MG, Callahan A, Goldstein LB, Zivin J, et al. : Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis : a secondary analysis of the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial. **Stroke 39** : 3297-3302, 2008
15. SSYLVIA study investigators : Stenting of symptomatic atherosclerotic lesions in the vertebral or intracranial arteries (SSYLVIA) : study results. **Stroke 35** : 1388-1392, 2004
16. The EC/IC Bypass Study Group : Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. **N Engl J Med 313** : 1191-1200, 1985
17. Wakhloo A, Mandell J, Gounis M, Brooks C, Linfante I, Winer J, et al. : Stent-assisted reconstructive endovascular repair of cranial fusiform atherosclerotic and dissecting aneurysms long-term clinical and angiographic follow-up. **Stroke 39** : 3288-3296, 2008