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Clinical and angiographic outcomes following endovascular treatment of very small (3 mm or smaller) intracranial aneurysm

A single-center experience

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Abstract

Treatments for very small (3 mm or smaller) intracranial aneurysms (VSAs) remain controversial. The aim of this study was to evaluate the efficacy of endovascular treatment for VSAs and to evaluate clinical risk factors associated with complications.

This retrospective study enrolled 82 VSA patients who underwent coil embolization in our institution. Angiographic outcomes were assessed according to the Meyers classification. The clinical results were evaluated using the modified Rankin scale (mRS) immediately after coiling, at discharge, and during follow-up. A Mann-Whitney *U* test was performed for non-normally distributed continuous variables. A Pearson χ^2 test or Fisher's exact test was performed for categorical variables.

Among 82 aneurysms, 54 were treated with stent-assisted coiling (SAC) embolization. Thromboembolic complications were seen in 2 patients (2.4%). Intraoperative rupture occurred in 4 patients (4.9%). Other adverse events occurred in 2 patients (2.4%). Two patients (2.4%) had permanent disabling neurologic deficit (mRS 3–6) because of complications. The overall mortality rate was 1.2%. Adverse events were correlated with the location of aneurysms ($P = .02$), Fisher grade ($P = .01$), and treatment experience ($P = .03$). Patients with middle cerebral artery (MCA) bifurcation and anterior communicating artery (ACoA) aneurysms were more likely to experience a higher incidence of complication. Thirty-five patients underwent angiographic follow-up. The complete occlusion rate improved from an immediate 37.8% to 80.0% at follow-up.

In the short term, coiling is a safe and effective approach for the treatment of VSAs. SAC may be associated with a high rate of further occlusion during short-term follow-up. Endovascular treatment of VSAs at middle cerebral artery bifurcation or anterior communicating artery is associated with a higher incidence of complications.

Abbreviations: ACoA = anterior communicating artery, DSA = digital subtraction angiography, MCA = middle cerebral artery, mRS = modified Rankin scale, PED = pipeline endovascular device, SAC = stent-assisted coiling, VSA = very small intracranial aneurysm.

Keywords: coil embolization, stent, very small aneurysm

1. Introduction

Very small intracranial aneurysms (VSAs), also known as tiny intracranial aneurysms, refer to those of 3 mm diameter or smaller aneurysms.[1–3] Recent advances in neuroimaging, especially the three-dimensional (3D) cerebral angiography, have increasingly improved the diagnosis rate for VSAs. With advances in endovascular techniques, endovascular coil embolization of intracranial aneurysms is considered a valid alternative to surgical clipping.[4] Nevertheless, VSAs usually pose particular technical challenges for the endovascular surgeons, and the safety of endovascular coiling for VSAs remains controversial.[1,5–7] The technique challenges include the inability to obtain a stable microcatheter position, and the increased risk of perforation related to placing coils into confined spaces. Additionally, the chance of procedural rupture might be higher during endovascular embolization.[1,5–10] Studies focusing on the outcome of endovascular coiling for VSAs are limited. The safety and effectiveness of stent-assisted coiling (SAC) in VSAs are not well known. In the present study, we conducted a retrospective single-center analysis on the safety and efficacy of endovascular coil embolization in VSA patients. In addition, we wish to ascertain whether stent-assisted technology has an impact on the progressive occlusion of VSAs.

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2. Materials and methods

2.1. Patient characteristics

The study was approved by the local Institutional Review Board and Ethics Committee. We retrospectively reviewed 451 patients who underwent endovascular treatment in our institution between July 2004 and June 2015, and a total of 481 intracranial aneurysms were intervened. The clinical profiles and radiological data were collected and analyzed. The Fisher grade was determined by the last CT scan before treatment. Among the 481 aneurysms, 87 of them in 87 patients were VSAs. Among the 87 VSAs, 5 aneurysms were treated by sole stenting. Eventually, 82 aneurysms in total in 82 patients were included in this study. The aneurysm is defined as wide-neck when the dome/neck ratio is $\leq$2.0.

Indications for endovascular treatment: (1) ruptured aneurysm, (2) additional aneurysm to another ruptured aneurysm, (3) presence of family history of subarachnoid hemorrhage, (4) irregular or multilobulated aneurysm, (5) multiple aneurysms, and (6) emotional distress for having an aneurysm.

2.2. Pharmacologic therapy protocol and endovascular procedures

Patients were premedicated with 100 mg aspirin and a loading dose of 75 mg clopidogrel for 2 to 3 days before stent-assisted embolization. For the stents used without premedication, 300 mg clopidogrel and 300 mg aspirin were administered via a naso/orogastric tube.

All of the coil embolization surgeries were performed under general anesthesia. The aneurysm size was measured on three-dimensional (3D) rotational angiography, or on two-dimensional (2D) angiography according to a reference calibration object taped to the patient's head.

A bolus of 3000 IU of heparin was administered after femoral arterial sheath placement and intermittent boluses of 1000 IU per hour were subsequently administered. As to wide-neck aneurysms, a stent-assisted technique (Enterprise stent, Codman Neurovascular; Neuroform stent, Boston Scientific; Solitaire stent, ev3) was required. Immediate angiographic results after coil embolization were assessed by 2 experienced neurointerventionists (YL and FW) independently. Disagreements were resolved by consensus. The aneurysm occlusion grade was evaluated according to the Meyers classification:[11] Grade 0, complete aneurysm occlusion; Grade 1, 90% or greater aneurysm occlusion; Grade 2, 70–89% aneurysm occlusion; Grade 3, 50–69% aneurysm occlusion; Grade 4, 25–49% aneurysm occlusion; and Grade 5, less than 25% aneurysm occlusion.

Periprocedural complications such as aneurysm ruptures or thromboembolic events were documented.

2.3. Follow-up data

Angiographic outcomes were assessed according to the Meyers classification. Changes in angiographic outcome were classified as follows: stable occlusion (no change in coil configuration, obliteration grade, or contrast filling), further occlusion (progressive occlusion or involution of the neck remnant or contrast filling in aneurysm), and recanalization (aneurysm recurrence evident due to neck growth, coil compaction, coil extrusion by aneurysm degradation, or new sac formation). During the follow-up period, angiographic evaluation with digital subtraction angiography (DSA) was performed at 3 to 6 months after endovascular treatment. If no recanalization evidence was observed, the subsequent angiographic evaluation was performed at 18 months after treatment.

Clinically, the neurological and functional status was evaluated according to the modified Rankin scale (mRS) immediately after coiling, at discharge, and during the follow-up period. Good outcomes were defined as an mRS score of 0–2; poor outcomes were defined as an mRS score of 3–6.

Table 1

Characteristics of patients with very small aneurysms and statistical analyses in stent-assisted coiling and nonstent-assisted coiling groups.

	Stent-assisted coiling (n=54)	Nonstent-assisted coiling (n=28)	*P*
Characteristics			
Female	28 (52)	16 (64)	.649*
Hypertension	28 (52)	16 (64)	.649*
Smoking, %	15 (28)	5 (18)	.321*
Median age, years	58.0	57.0	.30†
Angiographic results			.246*
Grade 0	18 (33)	13 (47)	
Grade 1–2	36 (67)	15 (53)	

Unless indicated otherwise, data are number of cases, with percentages in parentheses.
* χ^2 test.
† Mann–Whitney *U* test.

2.3.1. Statistical analyses.

SPSS 19.0 software (SPSS Inc., Chicago, IL) was used for statistical analyses. A Mann-Whitney *U* test was performed for non–normally distributed continuous variables. A Pearson χ^2 or Fisher's exact test was used to compare proportions. Probability (*P*) values $<.05$ were considered significant.

3. Results

The patient characteristics and the aneurysm features were summarized in Table 1. The cohort consisted of 38 males (46.3%) and 44 females (53.7%), with a mean age of 57.2 years (range, 20–81 years). Of the 82 VSAs, 50 (61.0%) were ruptured and 32 (39.0%) remained unruptured.

3.1. Initial angiographic manifestations

The locations of aneurysms (Table 2) included the internal carotid artery (n=49), middle cerebral artery (MCA) (n=5), anterior cerebral artery (n=20), and posterior circulation (n=8). Based on the post embolization angiographic studies (Table 1),

Table 2

Locations of very small aneurysms in the stent-assisted coiling and nonstent-assisted coiling groups.

Variable	Stent-assisted coiling (n=54)	Nonstent-assisted coiling (n=28)	Total (n=82)
Internal carotid artery	40 (74)	9 (32)	49
C4 segment	1	0	1
C5 segment	2	0	2
C6 segment	12	0	12
C7 segment	25	9	34
Middle cerebral artery	3 (6)	2 (7)	5
Anterior cerebral artery	6 (11)	14 (50)	20
Anterior communicating	4	14	18
A1 segment	2	0	2
Posterior circulation	5 (9)	3 (11)	8
Basilar artery	1	2	3
Posterior cerebral artery	2	1	3
Vertebral artery	2	0	2

Unless indicated otherwise, data are number of cases, with percentages in parentheses.

Table 3

Potential risk factors related to complications.

Variable	Ischemic events (n=2) Yes	Ischemic events (n=2) No	Intraoperative rupture (n=4) Yes	Intraoperative rupture (n=4) No	Other adverse events (n=2) Yes	Other adverse events (n=2) No	Cumulative adverse events (n=8) Yes	Cumulative adverse events (n=8) No	P
Sex									1.00*
Women	2 (5)	42 (95)	2 (5)	42 (95)	0 (0)	44 (100)	4 (9)	40 (91)	
Men	0 (0)	38 (100.0)	2 (5)	36 (95)	2 (5)	36 (95)	4 (11)	34 (89)	
Fisher grade									.01*
Grade I–II	0 (0)	35 (100)	0 (0)	35 (100)	0 (0)	35 (100.0)	0 (0)	35 (100)	
Grade III–IV	2 (4)	45 (96)	4 (9)	43 (91)	2 (4)	45 (96)	8 (17)	39 (83)	
Location									.02*
ACoA	1 (6)	17 (94)	1 (6)	17 (94)	1 (6)	17 (94)	3 (17)	15 (83)	
MCA bifurcation	0 (0)	5 (100)	1 (20)	4 (80)	1 (20)	4 (80)	2 (40)	3 (60)	
Other	1 (2)	58 (98)	2 (3)	57 (97)	0 (0)	59 (100)	3 (5)	56 (95)	
Stent placement									.44*
Yes	2 (4)	52 (96)	1 (2)	53 (98)	1 (2)	53 (98)	4 (7)	50 (93)	
No	0 (0)	28 (100)	3 (11)	25 (89)	1 (4)	27 (96)	4 (14)	24 (86)	
Treatment experience									.03*
Early phase (first 41 cases)	1 (2)	40 (98)	4 (10)	37 (90)	2 (5)	39 (95)	7 (17)	34 (83)	
Late phase (the other cases)	1 (2)	40 (98)	0 (0)	41 (100)	0 (0)	41 (100)	1 (2)	40 (98)	

Unless indicated otherwise, data are number of cases, with percentages in parentheses.
* χ^2 test or Fisher's exact test.

Grade 0 embolization was achieved in 31 of 82 aneurysms (37.8%). In the remaining 51 aneurysms, there was Grade 1 embolization in 47 (57.3%) and Grade 2 embolization in 4 (4.9%).

3.2. Stents used in treatment

Among 82 aneurysms, 54 aneurysms were treated with SAC. SAC was performed with the assistance of the Enterprise stent in 8 aneurysms, the Solitaire stent in 25 aneurysms, and the Neuroform stent in 21 aneurysms.

Table 4

Potential risk factors related to follow-up results.

Variable	Good outcome (n=58)	Poor outcome (n=6)	Total	P
Median age, years	57.0	56.5		.90*
Sex				1.000†
Women	30 (90)	3 (10)	33	
Men	28 (90)	3 (10)	31	
Fisher grade				.04†
Grade I–II	27 (100.0)	0 (0)	27	
Grade III–IV	31 (84)	6 (16)	37	
Location				.16†
Anterior communicating artery	13 (81)	3 (19)	16	
Middle cerebral artery bifurcation	3 (75)	1 (25)	4	
Other	42 (93)	3 (7)	45	
Stent placement				1.00†
Yes	38 (90)	4 (10)	42	
No	20 (91)	2 (9)	22	
Treatment experience				.21†
Early phase (first 41 cases)	30 (86)	5 (14)	35	
Late phase (the other cases)	28 (97)	1 (3)	29	
Adverse Events				.01†
Ischemic Events	0 (0)	2 (100.0)	2	
Intraoperative Rupture	3 (75)	1 (25)	4	
Other	55 (95)	3 (5)	58	

Unless indicated otherwise, data are number of cases, with percentages in parentheses.
* Mann-Whitney *U* test.
† χ^2 test or Fisher's exact test.

3.3. Adverse events and mortality

Adverse events are summarized in Table 3. Thromboembolic complications were seen in 2 patients (2.4%). Intraoperative rupture occurred in 4 patients (4.9%). Other adverse events occurred in 2 patients (1 case of gastrointestinal bleeding and 1 case of early repeat bleeding). Two patients (2.4%) had permanent disabling neurologic deficit (mRS 3–6) because of complications. One patient died due to gastrointestinal bleeding. The overall mortality rate was 1.2%.

Statistical analysis demonstrated that adverse events were correlated with the location of the aneurysms ($P=.02$), Fisher grade ($P=.01$), and the treatment experiences ($P=.03$). Patients with MCA bifurcation and anterior communicating artery (ACoA) aneurysms were more likely to have experienced a higher incidence of complications (Table 3).

3.4. Follow-up outcomes

Clinical follow-up data were available in 64 patients (Table 4). During a median follow-up period of 28.0 months (range, 3–124 months), no rebleeding occurred. Statistical analysis demonstrated that clinical outcomes were correlated with Fisher grade ($P=.04$) and adverse events ($P=.01$).

Angiographic follow-up was available in 35 patients with 35 aneurysms with a median follow-up period of 6.0 months (range, 3–100 months) (Table 5). Follow-up angiograms showed Grade

Table 5

Follow-up angiographic outcomes after stent-assisted coiling and nonstent-assisted coiling embolization.

Variable	Stent-assisted coiling (n=22)	Nonstent-assisted coiling (n=13)	P
Angiographic outcome			.08*
Grade 0	20 (91)	8 (62)	
Grade 1–2	2 (9)	5 (38)	
Changes in angiographic outcome			.01*
Recanalization	0 (0)	3 (23)	
Stable	8 (36)	8 (62)	
Further occlusion	14 (64)	2 (15)	

Unless indicated otherwise, data are number of cases, with percentages in parentheses.
* χ^2 test or Fisher's exact test.

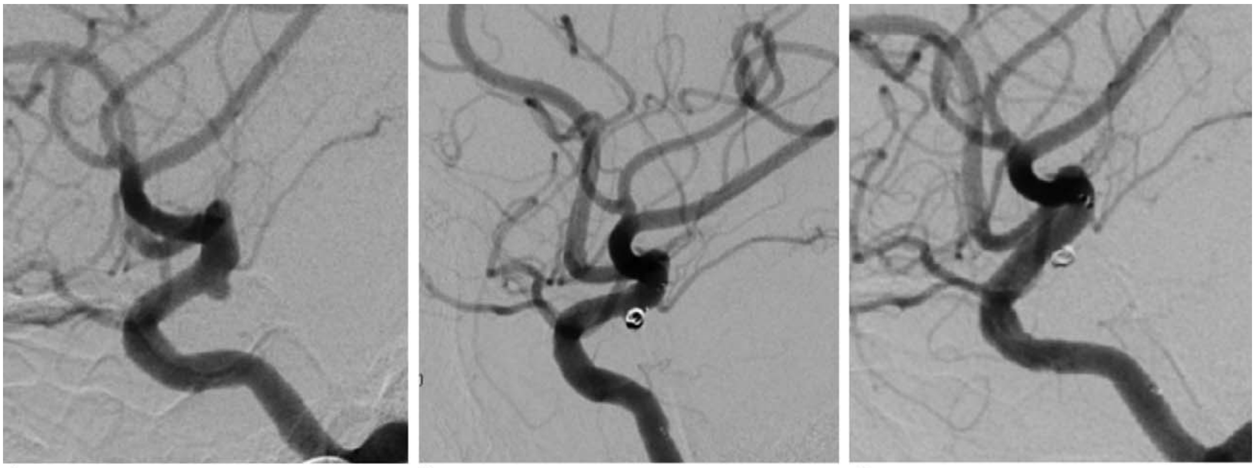

Figure 1. Coiling of a ruptured VSA in a 40-year-old woman with stent assistance. Cerebral angiography showed a VSA on the left internal carotid artery (A). Angiogram immediately after stent-assisted coiling (Solitaire) revealed Grade 1 embolization of the aneurysm (B). Follow-up angiographic examination at 22 months after embolization revealed complete occlusion of the aneurysm (C). VSA = very small intracranial aneurysm.

0 embolization in 28 (80.0%), Grade 1 embolization in 6 (17.1%), and Grade 2 embolization in 1 (2.9%). Stable occlusion was observed in 16 aneurysms (45.7%), further occlusion in 16 aneurysms (45.7%), and recanalization in 3 aneurysms (8.6%). Stent placement may enhance progressive occlusion of VSAs, despite of initial unsatisfied angiographic results (Fig. 1).

4. Discussion

Intracranial aneurysms with a diameter of ≤3 mm are generally defined as very small.[12] A lack of consensus exists among relevant landmark trials that support clear guidelines in the treatment of VSAs.[7] Due to the small size of VSAs, the limited operation space would greatly increase the challenge for neurosurgeons. The endovascular coiling of VSAs is associated with a relatively high risk of intraprocedural rupture rates.[1,13,14]

Yang et al[15] reported a total complication rate of 14.2% in a retrospective study of 211 wide-necked ruptured aneurysms. Song et al[16] reported total complication rates of 3% in a retrospective study of 606 unruptured aneurysms. In our study, the complication rate was 9.8% (8/82). The complete occlusion rate improved from an immediate 37.8% to 80.0% at follow-up. These results suggest that endovascular coiling is an effective and safe approach for the treatment of VSAs.

The microcatheter was prone to drop out of the aneurysmal sac during packing, and the difficulty of re-catheterization may also increase the risk of aneurysm rupture. Therefore, the excessive pursuit of an angiographically perfect coil embolization for VSAs might increase the risk of aneurysm rupture, especially for the ruptured lesions.[14,17,18]

In the current study, the complication rate (9.8%) was consistent with previous findings related to the management of VSAs.[1,5,6,13] Most patients achieved a good outcome. The procedure-related permanent morbidity rate was 2.4% (2 of 82), and the mortality rate was 1.2% (1 of 82). This could be related to the relatively lower total occlusion rate in our study.

The International Subarachnoid Aneurysm Trial suggests that incompletely coiled aneurysms may be more likely to rerupture than completely coiled ones, although the overall rate of rerupture after coiling is low.[19] A near-total occlusion of VSAs might result in less risk of aneurysm rupture, while the recurrence rate might be higher.

Experimental studies have demonstrated that stents have hemodynamic and biologic effects that can help the aneurysmal neck close.[8,20–23] However, the sequent antiplatelet therapy after stenting may increase the risk of recurrence.

In previous clinical studies, there have been conflicting results regarding the efficacy between SAC and non-SAC embolization. Some scholars demonstrated stent assisted technology for the treatment of aneurysms facilitated a higher coil packing density and a more stable aneurysm neck sealing.[9,22,24–26] However, Hwang et al[27] noted that stent placement provided no better long-term angiographic outcomes for aneurysms with an unfavorable configuration for coiling. Goddard et al[28] found that there was no definite relationship between the coil embolization ratio and aneurysm recurrence in small aneurysms.

The stent-assisted technology in the case of VSAs can be associated with an increased risk of perforations, as the stent may increase friction of the coil against the fragile aneurysm wall. In literatures, there are few data regarding the efficacy comparison of SAC and non-SAC in VSAs. The reported occlusion rates of aneurysms were quite variable, ranging from 42.5% to 89% in the stenting group, and from 5.3% to 42.8% in the nonstenting group.[10,22,27,29–33] In our cohort, progressive occlusion of incompletely coiled aneurysms was noted in 63.6% of aneurysms in the SAC group versus 15.4% in the non-SAC group ($P=.01$). Although about 66.7% of VSAs with SAC embolization in our series were incompletely occluded initially, 63.6% lesions progressed to complete occlusion. Thus, we speculate stent placement may promote the progressive occlusion of VSAs, despite initial unsatisfied angiographic results.

At the present time, studies focused on risk factors of complication during coil embolization for VSAs are limited.[34] Yang et al[15] reported a total complication rate of 18% in a retrospective study of 40 wide-necked ruptured VSAs. In our study, adverse events were correlated with the location of the aneurysms ($P=.02$), Fisher grade ($P=.01$), and treatment experience ($P=.03$). The inherent small diameter of the parent artery and complex anatomy of ACoA or MCA bifurcation aneurysms can make endovascular treatment difficult.[35–37] Yang et al[15] reported a total complication rate of 14% (26% in the ACoA group and 40% in the MCA bifurcation group) in a retrospective study of 211 wide-necked ruptured aneurysms. In our study, higher rates of the adverse events were observed in the ACoA group (16.7%) and in the MCA bifurcation group (40.0%). Neurosurgeons should be aware of these factors preoperatively to prevent complications.

In our study, clinical outcomes at follow-up were correlated with the Fisher grade ($P=.04$) and adverse events ($P=.01$). Likewise, other groups have reported that endovascular embolization of ruptured aneurysms was associated with increased morbidity and mortality.[9,15] Thus, the safety-efficacy profile of endovascular embolization is less favorable in higher grade hemorrhage patients with VSAs.

In our series, at a median of 28.0 months of follow-up, 2 of 2 patients had poor outcome following ischemic events during coil embolization, and 1 of 4 patients had poor outcome following intraoperative rupture during coil embolization. Intraoperative rupture is an urgent, serious, and life-threatening complication. A majority of patients can survive without severe sequelae if managed appropriately.[38] These results highlight the need to treat cerebral ischemia aggressively to maximize the chances of attaining an excellent outcome.[39]

The treatment techniques for intracranial aneurysm have been continually developing since the 1990s. This includes nanotechnology and pipeline endovascular device (PED).[40–42] In most series, the PED was used for the treatment of large or giant aneurysms. There are few data on the use of the PED in small aneurysms. Chalouhi et al[43] reported that the PED was a safe and effective alternative to conventional endovascular techniques for small aneurysms. There is a paucity of literature regarding the results of the PED for VSAs. The best endovascular technique for VSAs (i.e., coiling versus PED) is not clear.

4.1. Limitations

The sample size of the current study is still limited, and the retrospective design in a single center has its inherent demerits. Some patients did not undergo a long-term follow-up imaging study. Only 35 patients received angiographic follow-up, which may introduce bias. Further study with a larger number of patients and adequate follow-up would be necessary to validate our findings. The morphologies of enrolled VSAs were not absolutely the same in SAC and non-SAC groups. Therefore, there may be hidden factors that we had overlooked, which may influence the follow-up angiographic outcomes. In this study, we only included conventional endovascular techniques for VSAs. Further study is needed compare conventional endovascular techniques with PED to determine the best endovascular technique in this setting.

5. Conclusions

In the short term, endovascular coiling is an effective and safe approach for the treatment of VSAs. Additionally, embolization with the assistant of a stent seems to be associated with a higher rate of further occlusion during the short-term follow-up. Endovascular treatment of VSAs at middle cerebral artery bifurcation or anterior communicating artery is associated with a higher incidence of complications.

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