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# Late angiographic and clinical follow-up results of 100 consecutive aneurysms treated with Onyx reconstruction: largest single-center experience

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**Abstract** We present the long-term clinical and angiographic follow-up results of 100 consecutive intracranial aneurysms treated with Onyx liquid embolic system (MTI, Irvine, Calif.), either alone or combined with an adjunctive stent, in a single center. A total of 100 aneurysms in 94 patients were treated with endosaccular Onyx packing. Intracranial stenting was used adjunctively in 25 aneurysms including 19 during initial treatment and 6 during retreatment. All aneurysms except two were located in the internal carotid artery. Of the 100 aneurysms, 35 were giant or large/wide-necked, and 65 were small. Follow-up angiography was performed in all 91 surviving patients (96 aneurysms) at 3 and/or 6 months. Follow-up angiography was performed at 1, 2, 3, 4 and 5 years in 90, 41, 26, 6 and 2 patients, respectively. Overall, aneurysm recanalization was observed in 12 of 96 aneurysms with follow-up angiography (12.5%). All 12 were large or giant aneurysms, resulting in a 36% recanalization rate in the large and giant aneurysm group. One aneurysm out of 25 treated with the combination of a stent and Onyx showed recanalization. There was also no recanalization in the follow-up of small internal carotid artery aneurysms treated with balloon assistance only. At final follow-up, procedure- or device-related permanent neurological morbidity was present in eight patients (8.3%). There were two procedure-related and one disease-related (subarachnoid hemorrhage) deaths (mortality 3.2%). Delayed spontaneous asymptomatic occlusion of the parent vessel occurred in two patients, detected on routine follow-up. Onyx provides durable aneurysm occlusion with parent artery reconstruction resulting in perfectly stable 1-year to 5-year follow-up angiography both in small aneurysms treated with balloon assistance only (0% recanalization rate) and large or giant aneurysms treated with stent and Onyx combination (4% recanalization rate). Endosaccular Onyx packing with balloon assistance may not be adequate for stable long-term results in those with a large or giant aneurysm. However, the recanalization rate of 36% in these aneurysms is better than the reported results with other techniques, i.e., coils with or without adjunctive bare stents.

**Keywords** Intracranial aneurysm · Onyx · Long-term follow-up

## Introduction

Onyx (MTI, Irvine, Calif.), a liquid embolic system for the treatment of intracranial aneurysms, has been in clinical use since 1999 and further developed since then [1, 2]. The clinical results of Onyx treatment for intracranial aneurysms have been published in two articles [3, 4], one of which was a prospective, multicenter European study [4]. The use of Onyx involves placement of a balloon over the neck of the aneurysm while the material is injected endosaccularly. Following injection, the highly viscous material solidifies completely on diffusion of the DMSO solvent into the bloodstream [3–5].

We report the use of the material in 100 aneurysms and the long-term clinical and angiographic follow-up results to show the safety, effectiveness and durability of the material for the endovascular treatment of intracranial aneurysms.

## Methods and patients

This study included 100 consecutive aneurysms treated with endosaccular Onyx packing in 94 patients who agreed to have the Onyx treatment after signing an informed consent and to obey our strict angiographic follow-up protocol. The first 38 aneurysms in 36 patients have already been reported with their immediate, early and 1-year results in a multicenter prospective registry study [4].

Initially, patients in this study were selected on the basis of the CAMEO enrollment criteria [4]. The patients were required to have an aneurysm which (a) was likely to be difficult to treat or presented a high risk for conventional coil techniques and neurosurgical clipping, (b) had recurred following previous coil embolization, or (c) had failed prior surgical or endovascular treatment. These selection criteria were then modified by the authors during the evolution of their experience. During the course of enrollment, we observed very stable follow-up results in the initial cases, which encouraged us to use this technique in the treatment of small internal carotid artery (ICA) aneurysms as well. In this group the selection criteria for endosaccular Onyx packing were expanded such that any ICA aneurysm could be included, as long as: (1) there was no vessel originating from the aneurysm, (2) the aneurysm was not at the origin of the anterior choroidal or posterior communicating arteries, and (3) the ICA was not too large for the protection balloon to seal the aneurysm. Endosaccular Onyx packing is especially preferred as the method of choice when the aneurysm is shallow, large-necked or disproportionate in dimensions.

Baseline data were collected on the patients prior to the procedure, at the time of the procedure, at discharge and at 3 to 6 months and 1 year. Additional follow-up evaluation at 2 to 5 years was performed in many patients. Recorded clinical data included Glasgow Outcome score, modified Rankin score (mRS), cranial nerve deficits, any adverse events and any change from baseline neurological status. Outcomes regarding mass effect were recorded to determine whether the symptoms improved, remained the same or deteriorated. For the purpose of this paper the term "adverse events" means any clinical deviation from the patient's baseline health. It was also noted whether these were device-related, procedure-related, disease-related or unrelated.

### Patient group

The study included 94 patients with 100 aneurysms treated with Onyx between December 1999 and December 2003 in a single center. The patients' ages ranged between 6 and 71 years with a mean of 41 years. Of the 100 aneurysms, 16 were accompanied by subarachnoid hemorrhage (SAH). All 16 SAH patients were Hunt and Hess (H&H) grade 0, 1 or 2 at the time of treatment, except for 1 who was H&H grade 4. In six SAH patients the hemorrhage was within 1 month of treatment, and these were analyzed separately. Of the remaining ten aneurysms, four were recurrences which had undergone previous coiling in the acute phase. Of the aneurysms, 28 were incidental, and 72 were associated with symptoms including headache (65 aneurysms including patients with bleeds) and/or mass effect (21 aneurysms) or seizure (1 aneurysm). Four of the aneurysms were post-traumatic. In the entire series, seven aneurysms had undergone prior treatment, four with coils as mentioned above and three by craniotomy and wrapping.

All of the aneurysms were located at the ICA, except in one patient who had basilar tip and superior cerebellar artery aneurysms. The locations of the aneurysms are shown in Table 1.

Of the 100 aneurysms treated, 65 were small (<10 mm), 14 were large (10–25 mm) and 21 were giant (>25 mm). The majority (78%) were wide-necked with the neck ≥4 mm and/or a dome to neck ratio of <2. One aneurysm had a near fusiform neck. Table 2 shows the aneurysm sizes with respect to neck size and ratio.

**Table 1** The locations of the aneurysms

| Location | *n* |
|---|---|
| ICA | 98 |
| Petrous | 3 |
| Cavernous | 22 |
| Petrous/cavernous | 1 |
| Paraophthalmic | 68 |
| Posterior communicating artery[a] | 4 |
| Posterior circulation | 2 |

[a]These aneurysms are located at the site of posterior communicating artery, but the posterior communicating arteries do not fill with the ICA injection

**Table 2** The aneurysm sizes in relation to neck size

| Aneurysm size | Total | Neck <4 mm | Neck ≥4 mm | Neck ≥4 mm or dome-neck ratio <2 |
|---|---|---|---|---|
| Small (<10 mm) | 65 | 22 | 43 | 62 |
| Large (10–25 mm) | 14 | 0 | 14 | 14 |
| Giant (>25 mm) | 21 | 0 | 21 | 21 |
| *n* | 100 | 22 | 78 | 97 |

## Treatment technique

The fundamental technique used to embolize aneurysms with the liquid polymer, Onyx, in this series has been previously described [3, 4]. Where appropriate, we describe some technical variations with the evolution of the authors' experience.

All patients were treated under general anesthesia and full systemic anticoagulation with heparin. The balloon catheters utilized in this study were the DMSO-compatible Equinox and Hyperglide (Micro Therapeutics, Irvine, Calif.) and the microcatheter was the DMSO-compatible Rebar (Micro Therapeutics).

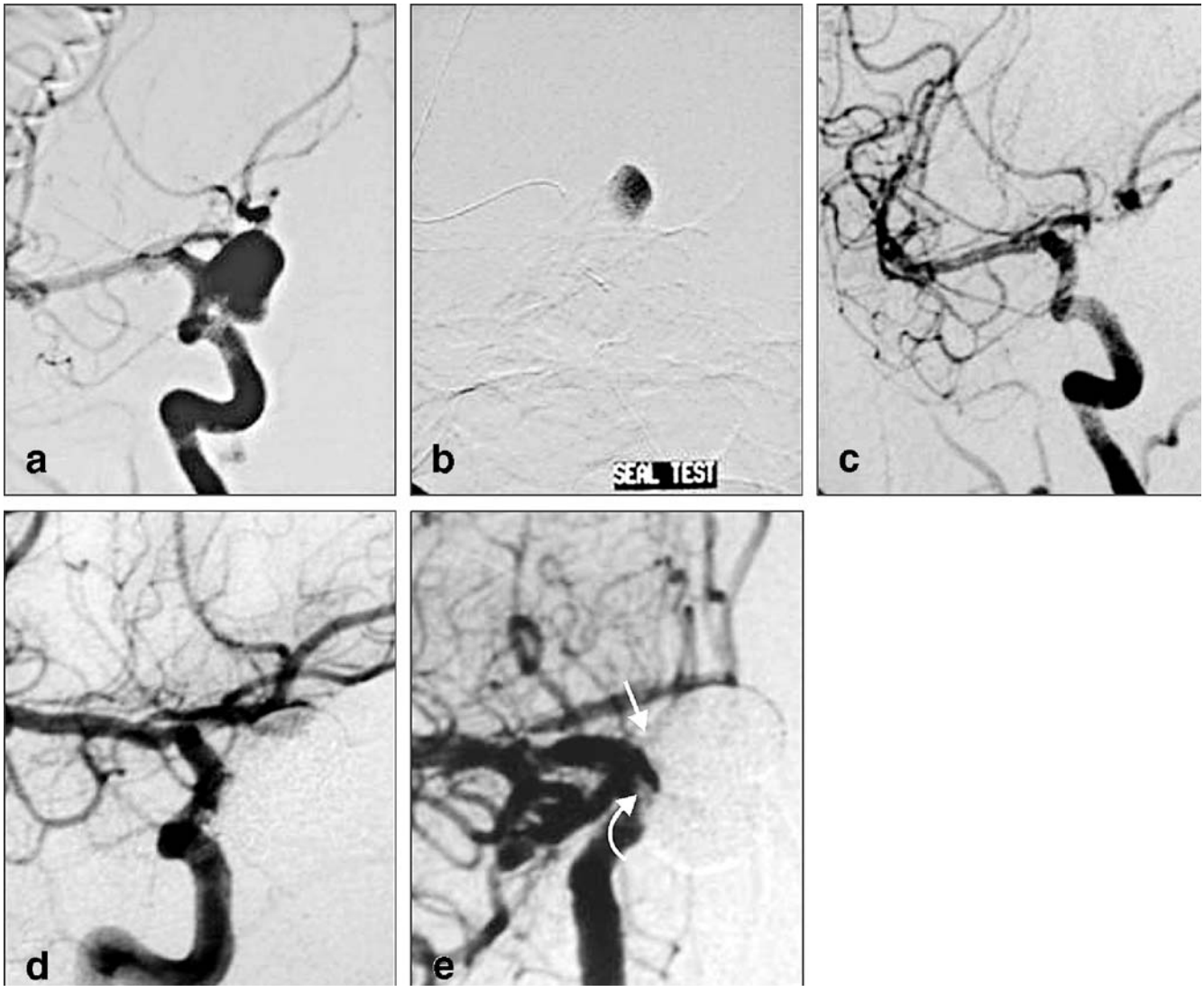


**Fig. 1** Large internal carotid aneurysm. **a** Prior to treatment. **b** "Seal test", prior to treatment of the aneurysm with Onyx. Microcatheter and balloon are in place with gentle injection of contrast agent into the aneurysm. **c** Angiographic result immediately after Onyx treatment. **d** Follow-up angiogram taken with the same working projection 4 years after treatment showing complete occlusion of the aneurysm. **e** Follow-up angiography at 4 years, A-P view, revealing Onyx circumscribing the parent artery (*arrows*)

With the balloon positioned and inflated over the aneurysm neck and the microcatheter in place within the aneurysm, contrast agent was slowly injected to ensure effective sealing of the aneurysm by the balloon (so-called 'seal test'; Fig. 1). The volume of contrast agent used in balloon inflation, which should be sufficient to seal the aneurysm neck, was noted, and during the procedure no less than this amount was put into the balloon in each Onyx injection. The use of Onyx treatment was basically dependent on two conditions: obtaining adequate control of the aneurysm neck with the balloon inflated and absence of a vessel coming off directly from the aneurysm sac in the seal test.

Following a 'successful' seal test, the microcatheter was first flushed with saline and the dead space was filled with DMSO. Onyx (HD 500) was injected slowly until the material approached the end of the microcatheter (usually 0.2 ml). Subsequently, the balloon was inflated and Onyx injected to fill the aneurysm sac for no longer than 3 min, unless there was a good collateral flow from the contralateral ICA or vertebral circulation. The injection process was facilitated by the use of a Cadence Precision Injector syringe (Micro Therapeutics, Irvine, Calif.), which allows precise injection of very small amounts. After the initial procedures, this injector syringe was modified; the so-called 'Quickstop' syringe releases the pressure within the microcatheter when the injection is ended and avoids further untoward material flowing into the aneurysm sac. After each injection, balloon inflation was maintained for another 2 min to ensure solidification of the Onyx material.

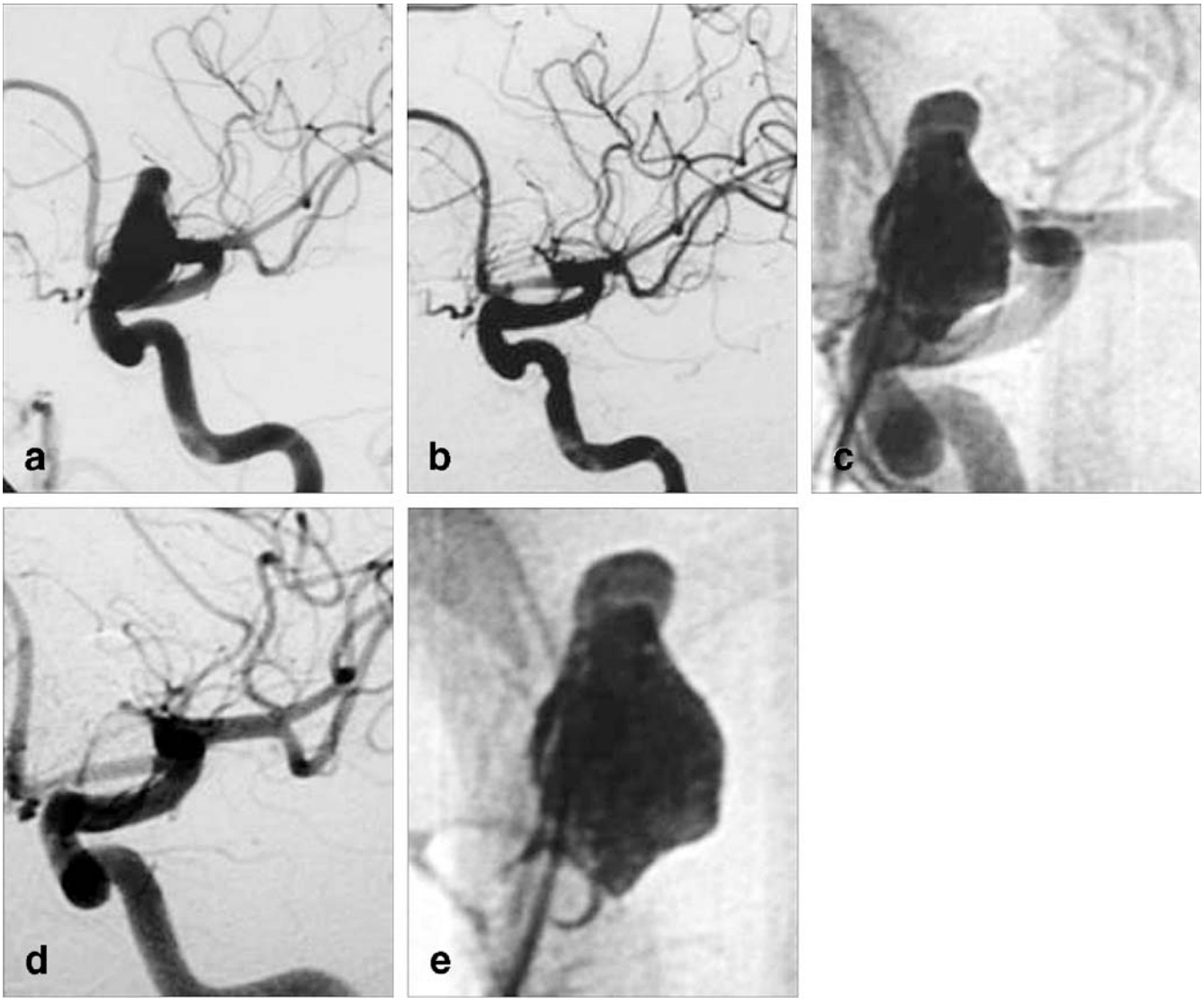


**Fig. 2** Large and partially thrombosed caroticoophthalmic aneurysm. **a** Prior to treatment. **b** Postembolization angiography showing complete occlusion. **c** Follow-up nonsubtracted angiography at 3 years showing reconstruction of the internal carotid artery with Onyx. **d** Follow-up angiography at 3 years showing complete occlusion of the aneurysm. **e** Onyx cast revealing crescent-like reconstruction of the parent artery

Between injection cycles, 2 min were allowed for cerebral perfusion.

As the aneurysm filled and the material approached the balloon, injection was paused frequently to allow the material to reconstruct the neck. In large or giant aneurysms, as the aneurysm enlarges, the neck represents an increasing proportion of the circumference of the parent vessel wall. In such cases the material should cover the aneurysm neck over the balloon during the procedure. As the material covered the neck it created a crescent-like reconstruction around the parent artery (Figs. 1e and 2), which ensured a complete and durable occlusion and reduced the risk of aneurysm recurrence.

Once it was confirmed angiographically that the aneurysm had been completely and satisfactorily occluded, the catheter syringe was decompressed by aspiration of 0.2 ml followed by a 10-min pause to allow complete solidification of the material with the balloon deflated. Following this step, the balloon was inflated and the microcatheter removed by gentle but brisk traction.

During the period of the study, a stent was placed across the neck prior to Onyx treatment in the same session as an adjunct in 25 aneurysms, including six retreatments. Stenting was indicated in order to achieve better reconstruction especially if the aneurysm was large or giant with a very wide neck in which the compliant remodeling balloon

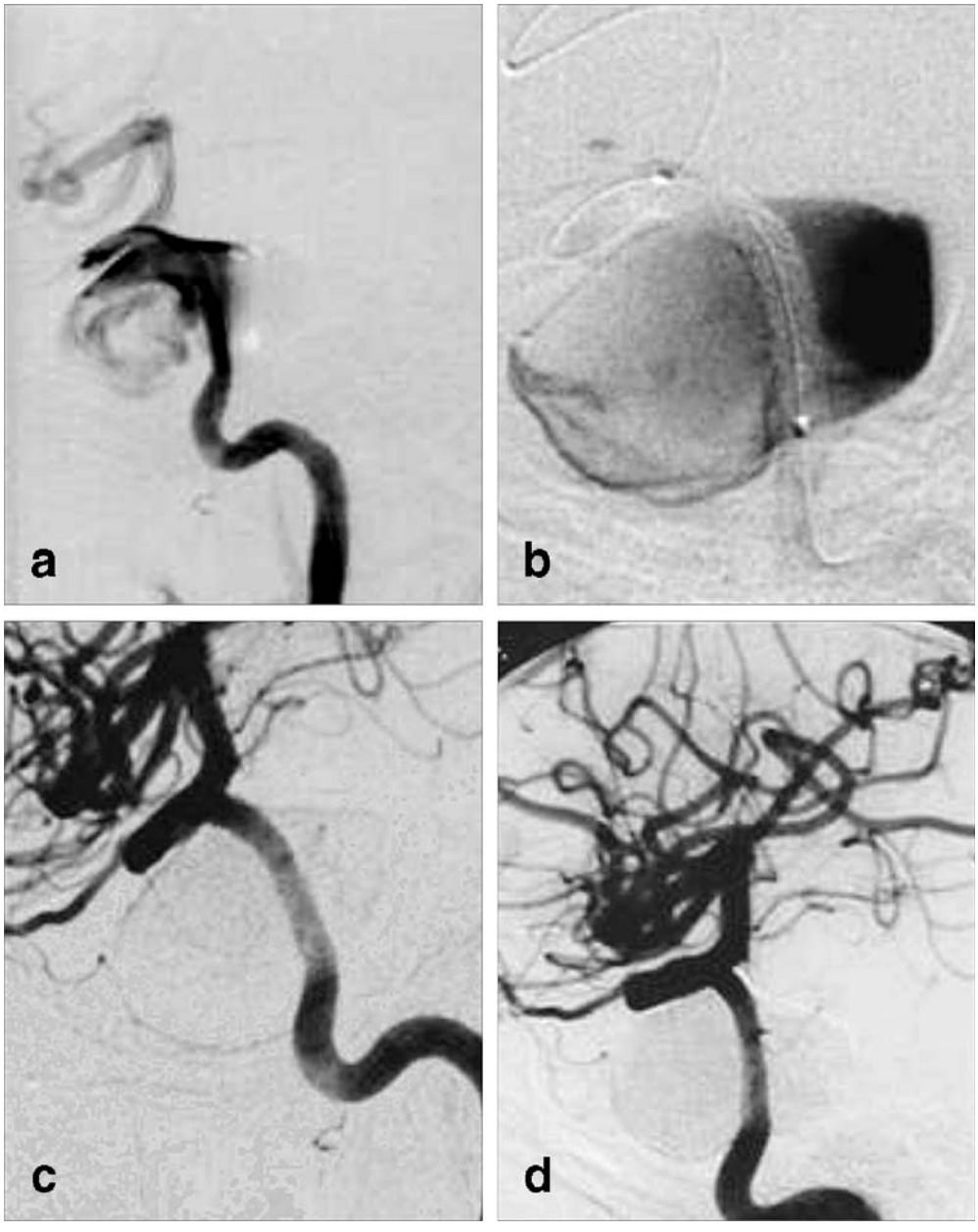


**Fig. 3** Giant cavernous very wide or fusiform necked ICA aneurysm in a 16-year-old girl. **a** Lateral view. **b** Seal test performed after inflation of the balloon of the stent placed across the aneurysm neck. Contrast agent is being injected into the aneurysm sac via a microcatheter placed in the aneurysm through one of the stent meshes. **c** Immediate lateral angiogram after treatment revealing excellent reconstruction of the ICA with complete aneurysm occlusion. **d** Follow-up angiography at 3 years demonstrating stable occlusion

**Table 3** Angiographic outcomes of 100 aneurysms: immediate, 3 to 6 months, 1 year and 2 to 5 years

| Angiographic results | Aneurysms/patients | Small (<10 mm) | Large (10–24 mm) | Giant (>25 mm) |
|---|---|---|---|---|
| Postembolization | 100/94 | *n*=65 | *n*=14 | *n*=21 |
| Complete occlusion (100%) | | 63 (97%) | 11 (78%) | 16 (76%) |
| Subtotal occlusion (90–99%) | | 2 (3%) | 3 (22%) | 4 (19%) |
| Incomplete occlusion (<90%) | | 0 | 0 | 1 (5%) |
| Follow-up at 3 to 6 months[a] | 96/91 | *n*=63 | *n*=13 | *n*=20 |
| Complete occlusion (100%) | | 63 (100%) | 8 (62%) | 13 (65%) |
| Subtotal occlusion (90–99%) | | 0 | 0 | 2 (10%) |
| Incomplete occlusion (<90%) | | 0 | 5 (38%) | 5 (25%) |
| Follow-up at 12 months (after retreatment when applicable) | 95/90 | *n*=62 | *n*=13 | *n*=20 |
| Retreatment of recanalized aneurysms in the 3- to 6-month follow-up[b] | | No retreatments | Retreatment of 3 of 5 recanalized aneurysms | Retreatment of 3 of 7 recanalized aneurysms |
| Complete occlusion (100%) | | 62 (100%) | 11 (84%) | 16 (80%) |
| Recanalized (subtotal/incomplete occlusion) | | 0 | 2 (16%) | 4 (20%) |
| Follow-up at 2 to 5 years[c] | | *n*=33 | *n*=11 | *n*=14 |
| Complete occlusion (100%) | | 33 (100%) | 11 (100%) | 13 (93%) |
| Recanalized (subtotal/incomplete occlusion)[d] | | 0 | 0 | 1 (7%) |

[a]After three deaths (four aneurysms)
[b]Six of the 12 recanalized aneurysms were treated with stent and Onyx combination
[c]For each patient after 12 months the latest follow-up angiography was taken into account
[d]Among six remaining recanalized aneurysms, five were treated with other methods and one was still being followed at the time of this report

prolapsed into the aneurysm sac (Fig. 3). In this study, AVE S670 (Medtronic/AVE), R (Orbus, The Netherlands) or Bx Velocity/Sonic (Cordis Endovascular, Miami Lakes, Fl.) coronary balloon expandable stents were used. We found the balloons of these stents to be compatible with Onyx by in vitro testing. Therefore, when the stent was deployed across the aneurysm neck, the balloon of the stent could be kept in place and used for the seal test and further Onyx injection. In another four large or giant aneurysms, the initial intention was to treat the aneurysm with the stent and Onyx combination; however, the attempt to place a stent failed due to difficulties in navigation. These four aneurysms were treated with Onyx alone.

The degree of aneurysm occlusion was recorded following the procedure and at the follow-up angiography. These results are shown in Table 3.

Immediately after the treatment cranial CT was performed to rule out any intracranial hemorrhage. Post-operative medical management evolved with experience during the study. We suggest the following as the medical regimens depending on whether a stent and/or an Onyx crescent was present at the parent artery wall interface. In the group in whom a stent was placed or a crescent of Onyx was layered at the wall of the parent artery at the neck: (1) intravenous heparinization is continued until the next day (unless contraindicated); (2) clopidogrel at a loading dose of 300 mg, is administered immediately after embolization followed by 75 mg daily (after the clinical and angiographic follow-up at 6 months, the clopidogrel can be stopped); and (3) oral acetylsalicylic acid (ASA) 300 mg is given daily for at least 6 months. In the group of patients with no stent or Onyx at the parent artery: (1) subcutaneous or intravenous heparinization is continued until the next morning; and (2) oral ASA 300 mg is given for 1 month.

## Results

This study involved 106 Onyx procedures in 94 patients to treat 100 aneurysms; six patients underwent re-treatment with stent and Onyx combination.

Table 3 shows the angiographic results at the end of the procedure, and at follow-up at 3 to 6 months, 1 year and 2 to 5 years. Complete occlusion was achieved in 90 out of 100 aneurysms treated, with an overall success rate of 90% at the end of the procedure. According to the aneurysm size, 63 of 65 small aneurysms (97%), 11 of 14 large aneurysms (79%) and 16 of 21 giant aneurysms (76%) were occluded totally. Except for one aneurysm in which the treatment was incomplete (occlusion <90%), the remaining nine aneurysms were subtotally occluded (i.e., 90–99%).

Table 4 shows baseline clinical status of the patients together with the clinical outcome at the 3- and 12-month follow-ups. The results were graded by means of the mRS, and the patients graded as mRS 2 or better (i.e., independent) were indicated. Table 4 also shows those patients who had a

**Table 4** Baseline clinical status and clinical outcome at 3 and 12 months

| | | Unruptured and other (*n*=88) | Recent SAH (*n*=6) |
|---|---|---|---|
| At baseline | | | |
| mRS | ≤2 | 83 | |
| H&H | 1 or 2 | | 5 |
| | 4 | | 1 |
| At discharge | | *n*=88 | *n*=6 |
| mRS | ≤2 | 79 | 5 |
| mRS | Unchanged/ improved | 78 | 5 |
| mRS | Worsened | 8 | – |
| Death before discharge | | 2 | 1 |
| At 3- to 6-month clinical follow-up (in 91 patients) | | *n*=86 | *n*=5 |
| mRS | ≤2 | 84 | 5 |
| mRS | Unchanged/ improved | 86 | 5 |
| mRS | Worsened | 0 | 0 |
| Death from discharge to 3–6 months | | 0 | 0 |
| At 12-month follow-up (in 90 patients, with retreatment as applicable) | | *n*=85[a] | *n*=5 |
| mRS | ≤2 | 85 | 5 |
| mRS | Unchanged/ improved | 85 | 5 |
| mRS | Worsened | 0 | 0 |
| Death from 3 to 12 months | | 0 | 0 |

[a]One patient had pancreatic cancer after the 6-month follow-up angiography and was then lost to follow-up

worsened dependency score compared with their baseline assessment. Permanent or transient adverse events were recorded in 14 patients (based on the definitions in the Methods and Patients section). Table 5 shows the adverse events, permanent or transient, with neurological consequences and Table 6 lists the mortalities in the entire series. Altogether, procedure-/device-related adverse events resulted in permanent neurological deficit in eight patients, i.e., the morbidity was 8.5%. Among these, two patients resulted in dependent survival (mRS 4) and the remaining six patients were mRS 2 or better (i.e., independent). There were also six transient neurological adverse events (6.4%) which resolved completely (Table 5).

A total of three patients died before discharge in this series for a mortality of 3.2% (Table 6). Two deaths were procedure-related events: one was a groin complication in a hemophiliac patient causing uncontrollable retroperitoneal bleeding; the second was a delayed parenchymal and subdural hematoma likely associated with vessel dissection/perforation during stenting. In the remaining patient (acute SAH group, H&H grade 4), the cause of death was disease-related pulmonary complications.

Overall, excluding six patients who were treated in the acute stage of subarachnoid hemorrhage, 83 of 88 patients had mRS ≤2 at baseline, and at discharge 79 patients had mRS of 2 or better. Eight patients (9.1%) deteriorated and two patients (2.3%) died in this group. At the 3- to 6-month follow-up among the remaining 86 patients, 84 had mRS of 2 or better with some patients improving since discharge; no patients showed any deterioration after discharge. One patient who had pancreatic cancer was lost to follow-up. At 12 months, all remaining 85 patients had mRS ≤2.

In the group of patients with acute subarachnoid hemorrhage, the baseline clinical status was recorded as H&H grade 1 or 2 in five and grade 4 in one. All five patients were discharged home with mRS 2 or better with no deterioration and remained unchanged or improved at the later follow-ups. The remaining patient, who was H&H grade 4, died prior to discharge as noted above.

Table 7 indicates the results of aneurysm treatment on mass effect of the aneurysm and the outcome at follow-up.

As for cranial nerve palsies, 15 patients presented with oculomotor palsies. In 11 of these the condition had completely resolved and 2 showed improvement at the 12-month follow-up. One remained unchanged and one showed deterioration. Six patients had optic nerve compression prior to treatment. At the 12-month follow-up, this condition had fully resolved in five patients and was worse in one patient.

A total of 65 patients presented with headache recorded as mild or moderate in 58 and severe in 7. At discharge, in 44 of the 58 patients, the headache had improved or

**Table 5** Serious adverse events with neurological morbidity

| Patient age/sex | Size and location of aneurysm | Description and cause of event | Baseline mRS | Outcome of event and mRS at latest follow up |
|---|---|---|---|---|
| Permanent morbidity | | | | |
| 39/M | Large carotid ophthalmic | Ipsilateral visual loss due to leak in ophthalmic artery | 0 | mRS 1, ongoing |
| 42/F | Giant carotid cavernous | Worsening of third, fourth, fifth and sixth cranial nerve palsy, resolution of fifth | 1 | mRS 1 |
| 57/F | Large posterior communicating artery | Worsening of third nerve palsy | 0 | mRS 1 |
| 75/F | Giant carotid cavernous | Total ophthalmoplegia | 1 | mRS 4 |
| 44/M | Giant carotid ophthalmic | Worsening of second nerve palsy | 1 | mRS 1, recovered to status at presentation |
| 56/M | Giant carotid ophthalmic | Worsening of third nerve palsy | 1 | mRS 1 |
| 45/F | Large cavernous | Worsening of sixth nerve palsy | 0 | mRS 1 |
| 51/F | Large carotid ophthalmic | Developed right MCA infarct 3 days after treatment; caused left arm monoplegia after stent/Onyx treatment | 1 | mRS 4, partial resolution by 1 year |
| Transient neurological morbidity | | | | |
| 42/F | Large carotid ophthalmic | Worsening visual symptoms which subsequently improved | 0 | mRS 1, completely resolved |
| 47/F | Large paraophthalmic | Developed transient hemiparesis | 0 | mRS 0, resolved |
| 57/F | Large cavernous | Intraprocedural thrombus in left ICA, hemiparesis and aphasia resolved by thrombolysis | 0 | mRS 1, resolved by day 1 |
| 34/F | Large carotid ophthalmic | Transient hemiparesis | 0 | mRS 0, resolved |
| 63/F | Large cavernous | Postprocedural thrombus in right ICA, hemiparesis; resolved immediately by thrombolysis | 0 | mRS 1 |
| 31/F | Large carotid ophthalmic | Transient hemiparesis | 0 | mRS 0, resolved |

resolved. In 8 it remained unchanged, and in four it had deteriorated. Two in this group died before discharge. At the 12-month follow-up, one patient was still suffering from headache with the remaining 54 patients having no headache. One was lost to follow-up after 6 months. Five of the seven patients who presented with severe headache were either pain-free or their headache had improved significantly. In one the headache remained unchanged at discharge (note: one patient in this subgroup died before discharge). None of these six patients had headache at the 12-month follow-up.

## Angiographic results at follow-up and retreatments

Follow-up angiography was obtained at 3 and 6 months in 91 patients with 96 aneurysms who were available for follow-up excluding three patients who died during the first admission. Two patients, with one aneurysm each, had delayed asymptomatic parent artery occlusion (PAO) discovered at the 6-month follow-up. These two patients had been treated only with Onyx and both of them had Onyx layering on the parent artery for the so-called 'crescentic' reconstruction. Before its detection, neither of these patients had any symptoms of PAO, and neither was receiving extended anti-platelet therapy (ASA and clopidogrel). These factors are elaborated in the discussion.

Follow-up angiography was performed at 1 year in 90 patients with 95 aneurysms including the two aneurysms with spontaneous PAO that were examined by MRA. One patient was lost to follow-up after the 6-month follow-up angiography; the patient had a diagnosis of pancreatic cancer.

Table 3 summarizes the angiographic outcomes of the aneurysms at follow-up. At the 3- to 6-month follow-up,

**Table 6** Fatalities during study period

| Patient age/sex | Size and location of aneurysm | Interval to death | Related to | Baseline mRS or H&H | Cause of death |
|---|---|---|---|---|---|
| 49/M[a] | Small basilar termination recurrent after prior coiling | 4 weeks | Disease-related | SAH 4 | Prior coil treatment, rebleeding, poor grade, and died from pulmonary complications |
| 30/F | Large ICA (posterior communicating) | 5 days | Stent-related dissection and delayed rupture | 0 | Initially intact, after procedure developed temporal and subdural hematoma. Suddenly deteriorated with fixed pupils |
| 67/F | Giant ICA cavernous | 2 days | Procedure-related | 0 | Hemophiliac patient, groin hematoma and uncontrollable retroperitoneal hematoma |

[a]This patient had two aneurysms: basilar termination and superior cerebellar artery aneurysms

**Table 7** Results of treatment on mass effect

| | Baseline | At discharge | 12-month or latest follow-up |
|---|---|---|---|
| Optic nerve compression | | | |
| No. of patients | 6 | | |
| Resolved | | 3 | 5 |
| Unchanged | | 2 | 0 |
| Worsened | | 1 | 1 |
| Oculomotor deficits | | | |
| No. of patients | 15 | | |
| Resolved | | 3 | 11 |
| Improved | | | 2 |
| Unchanged | | 7 | 1 |
| Worsened | | 5 | 1 |
| Headache (mild/moderate) | | | |
| No. of patients[a] | 58 | | |
| Improved/resolved | | 44 | 54 |
| Unchanged | | 8 | 1 |
| Worsened | | 4 | 0 |
| Headache (severe) | | | |
| No. of patients[b] | 7 | | |
| Improved/resolved | | 5 | 6 |
| Unchanged | | 1 | 0 |
| Worsened | | 0 | 0 |

[a]Two patients died prior to discharge; one patient was lost to follow-up at 12 months
[b]One patient died prior to discharge

there was recanalization or residual aneurysm in 12 out of 96 aneurysms with follow-up angiography, i.e., 12.5% overall recanalization rate. Small aneurysms which were completely occluded at the end of the procedure (63 aneurysms) remained totally occluded with no recanalization or regrowth in the first follow-up angiography at 3 or 6 months (recanalization 0%). This result was stable at 1 year and following later follow-up angiography as well (Figs. 4 and 5). However, in the large or giant aneurysm group, 6 of 27 of the completely occluded aneurysms showed recanalization (22%). Overall, 21 of 33 of the large or giant aneurysms were totally occluded (64%) at the first follow-up angiography at 3 to 6 months. All 12 recanalized aneurysms were giant (7) or large (5), so the recanalization rate in the combined large and giant group was 36%. Of the 12 recurrent aneurysms, 6 were retreated with Onyx combined with an adjunctive stent. In the other 6, retreatment was not completed until the 12-month follow-up.

At the 12–month follow-up angiography, including retreated patients, 89 out of 95 aneurysms which had angiographic follow-up (including two with MRA) showed complete occlusion (94%). In the large or giant aneurysm group, 27 of 33 aneurysms were totally occluded (82%). Five of the six residual aneurysms noted at the 12-month follow-up angiography were treated with other methods, i.e., PAO in two, surgical bypass and PAO in two and covered stent in one. The remaining one residual aneurysm with no further treatment was still being followed at the time of this report and had not shown any enlargement since the initial follow-up angiography. Angiographic follow-up was obtained at 2, 3, 4 and 5 years in 41, 26, 6, and 2 aneurysms, respectively. All aneurysms which had

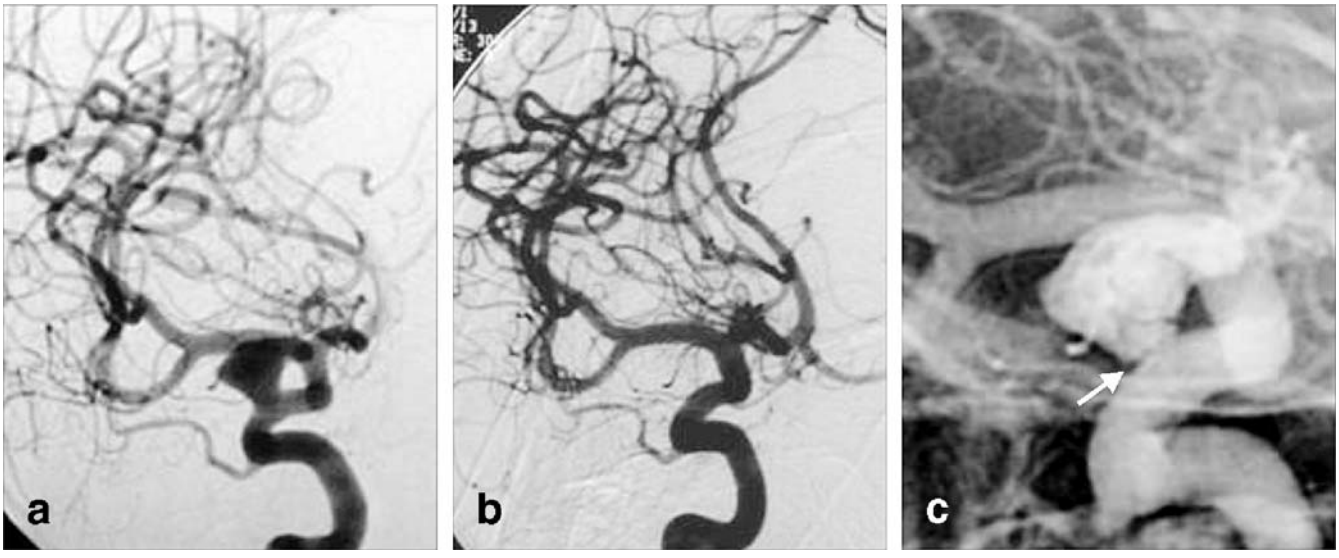


**Fig. 4** Caroticoophthalmic aneurysm associated with SAH. **a** Before treatment. **b** Follow-up angiography 2 years after Onyx treatment shows complete occlusion of the aneurysm and reconstruction of the ICA. **c** Follow-up angiography at 2 years, nonsubtracted view, reveals smooth healing reaction across the aneurysm neck (*arrow*)

follow-up angiography after 1 year remained stable in the later follow-ups including retreatments.

On subgroup analysis only one patient treated with the stent and Onyx combination showed any recanalization, for a complete occlusion rate of 96% (24/25). In the subgroup of large or giant aneurysms treated without a stent, recanalization developed in 11 out of 16 aneurysms at the 3- to 6-month follow-up (69%) (Fig. 6).

When recurrence of the aneurysm occurred it was always seen in the 3 or 6-month follow-up angiogram; it should also be noted that no further recanalization or regrowth occurred after 3 to 6 months in the entire group. There was no rebleeding in any of the patients in our series during a follow-up of up to 5 years.

## Discussion

The publication of the results of the International Subarachnoid Aneurysm Trial (ISAT) strongly reinforced the fact that endovascular treatment with detachable platinum coils is a safe and effective treatment for ruptured intracranial aneurysms [6]. A second result of that study was that endovascular treatment is relatively more

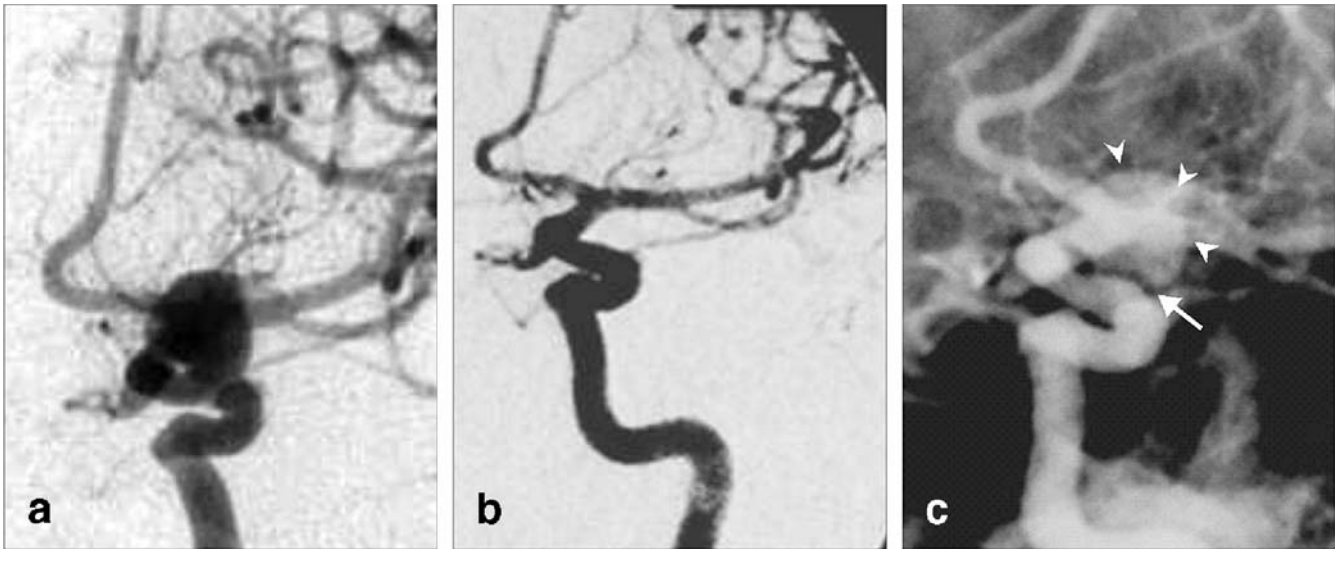


**Fig. 5** Left caroticoophthalmic aneurysm. **a** Before treatment, oblique view. **b** Follow-up angiography at 1 year shows complete occlusion of the aneurysm. **c** Follow-up angiography at 1 year, nonsubtracted view, reveals the aneurysm completely occluded with Onyx (*arrowheads*) and parent artery reconstruction with a smooth layer of healing reaction (*arrow*) across the neck

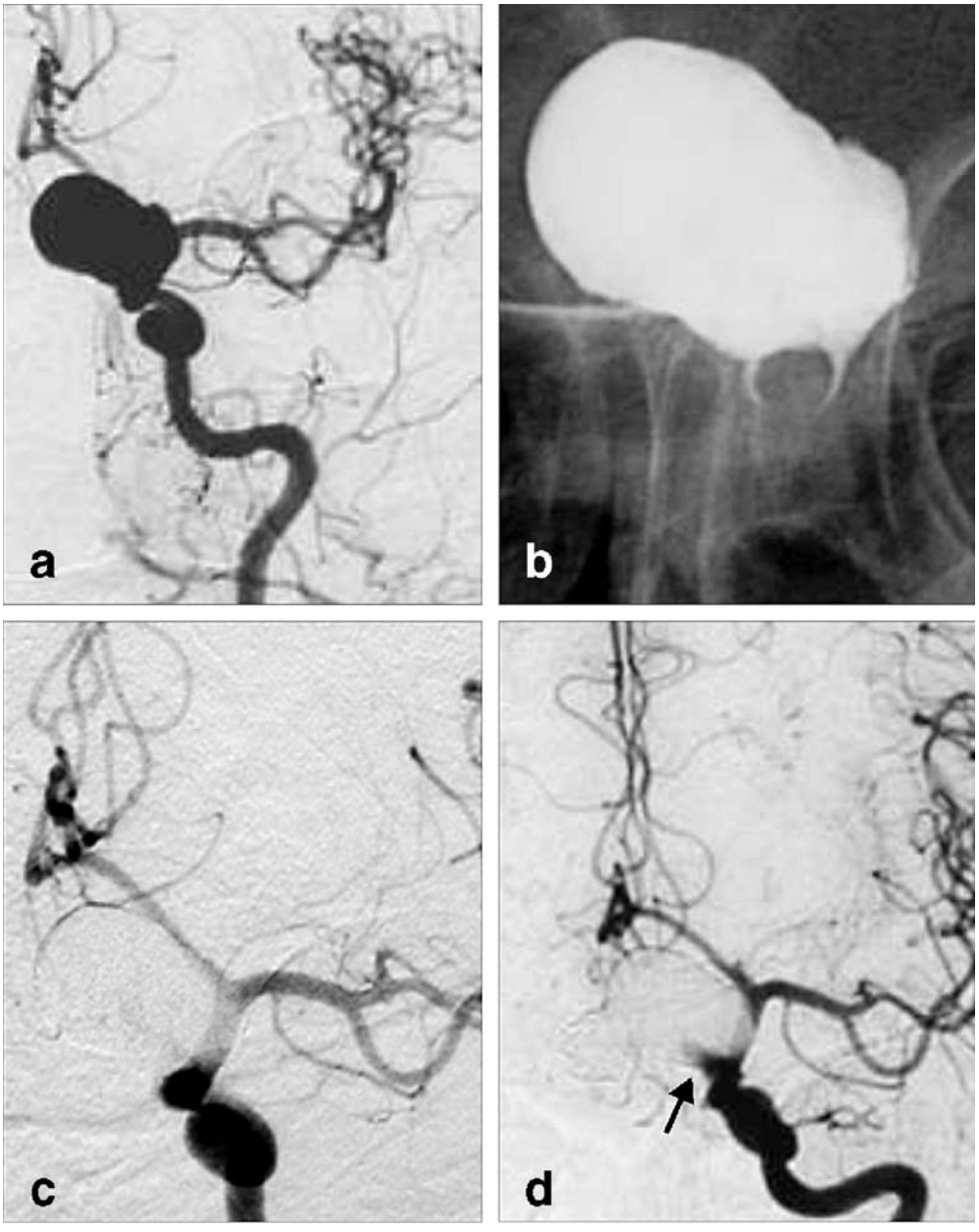


**Fig. 6** Giant, partially thrombosed left caroticoophthalmic aneurysm. **a** A-P view before treatment. **b** Post-treatment Onyx cast, A-P view, showing excellent reconstruction of the parent artery without a stent that could not be placed across the neck. **c** Post-treatment angiography, A-P view. **d** Follow-up angiography at 1 year, A-P view, revealing aneurysm regrowth (*arrow*) despite good neck reconstruction (**b**, **c**)

successful in terms of clinical outcome at 1 year compared to surgical treatment for patients with small ruptured anterior circulation aneurysms (if suitable for endovascular treatment). That study, however, did not address the issue of large/giant or unruptured aneurysms.

Unruptured aneurysms were examined in the International Study of Unruptured Intracranial Aneurysms (ISUIA) [7, 8]. Data from that study indicated that surgical management of unruptured aneurysms generally has a poor clinical outcome based on combined mRS 3–6 and/or the cognitive deficits seen at 1 year. Importantly, the poor outcome rate was 25% for large and 34% for giant aneurysms [8].

In our series, the poor outcome rate was 10% at discharge in the entire unruptured group, including 2% mortality. In addition, the overall poor outcome rate at 3 to –6 months in this group was 4.6%. All permanent complications occurred in the large and giant aneurysm group where the overall morbidity rate was 20% (7/35). In this same group, however, the poor outcome (mRS >2) rate was only 11% including 6% mortality at 3 to 6 months.

Coil treatment of large and giant aneurysms has been examined by several authors [9–11]. All have found poor long-term outcomes. Sluzewski et al. reported a good clinical outcome in 79% of large and giant aneurysms treated by coiling [10]. In that study, however, incomplete

occlusion was noted in 69% of aneurysms (20/29) at follow-up. In addition, 12 of 29 aneurysms (41%) remained incompletely occluded following repeated endovascular treatment. These required surgical treatment or parent vessel occlusion. Gruber et al. achieved a complete or subtotal occlusion rate of 71% of large and giant aneurysms [10]. However, these authors did note the requirement for multiple endovascular procedures since the single endovascular treatment success rate was only 12.5% for giant and 31% for large aneurysms.

Murayama et al. at UCLA reported complete occlusion at the end of the treatment in 40% and 26% of large and giant aneurysms, respectively [11]. They reported a recanalization rate of 20.9% in the entire series of aneurysms, and for large and giant aneurysms the recanalization rates were 35% and 59.1%, respectively. However, these numbers included only the aneurysms which showed further regrowth at follow-up but excluded the stable residua.

In our large and giant aneurysm group, complete occlusion was achieved in 79% and 76% of the aneurysms, respectively, at the end of the treatment. In this subgroup, recanalization was noted in 22% of the completely occluded aneurysms at the time of treatment and 36% overall (note that these numbers included all aneurysm filling, regardless of the residuum being stable or increasing). Moreover, in the entire series the overall recanalization rate was 12.5% and all recanalized aneurysms in this series belonged to the large and giant aneurysm group. These results are far better than those mentioned above [9–11]. Of the 12 recanalized aneurysms, 6 were retreated with the stent and Onyx combination and none of these aneurysms recurred in the long term.

Stents have been used in association with coils to treat wide-necked aneurysms that cannot be treated by coiling alone or with balloon assistance in order to obtain a more stable aneurysm occlusion [12, 13]. However, there is still a considerable rate of incomplete occlusion with the stent and coil combination resulting in recanalization of 20% of complicated aneurysms in follow-up studies.

In large and giant aneurysms, the parent artery is also diseased together with the aneurysm sac, since the neck often involves an increasing proportion of the circumference of the parent vessel wall. This may also provide a clue as to why larger aneurysms which have a wider neck have relatively worse angiographic results. In such large or giant aneurysms, occluding the aneurysm sac effectively and also treating the diseased vessel wall adjacent to the aneurysm neck is necessary. Therefore, different techniques and materials for better and more durable reconstructive treatments are needed.

The aims of treatment with the Onyx liquid embolic system are to fully reconstruct the parent vessel wall and permanently close the aneurysm. The use of Onyx for cerebral aneurysm treatment, both with or without a stent, has been recently reported in the literature [3, 4]. These studies have shown that Onyx can produce durable aneurysm occlusion in patients with difficult large and giant wide-necked intracranial aneurysms where other endovascular techniques are likely to fail and where surgery carries substantial morbidity. According to the multicenter, prospective CAMEO study, the clinical results and complication rates of endovascular aneurysm treatment with Onyx appear comparable with those of other endovascular techniques in similar patient populations; however, the final complete occlusion rate of 79% appears significantly better than those reported for large and giant aneurysms following coil treatment [4].

In our series, the complete occlusion rate was 87.5% at 3 to 6 months and 93% at 12 months, including six retreatments. However, there is an important difference between our single-center experience and the CAMEO study series [4]. Initially, we had selected patients according to the CAMEO study criteria (the first 36 patients included in the CAMEO trial) including large or giant aneurysms that were likely to be difficult to treat, presented a high risk for conventional coil techniques and neurosurgical clipping, or had failed prior surgical or endovascular treatment. Our selection criteria were then modified based on our experience. Since very stable and reconstructive follow-up results were obtained that were superior to those following coiling, especially for the small ICA aneurysms, we have increasingly started to use Onyx reconstruction for ‘coilable’ caroticoophthalmic or posterior wall ICA aneurysms, endovascular treatment of which requires balloon remodeling in our opinion. This group also provided the most durable results of our study with a 0% recanalization rate (Fig. 4). In all of these small ICA aneurysms, a fine smooth layer of intimal reaction of varied thickness between the neck of the aneurysm and parent artery was observed (Figs. 4c and 5). This created an important difference in that, while large or giant aneurysms constituted 80% of the CAMEO series, our series included only 35% large or giant aneurysms. Although the overall complete occlusion rate in our series was higher than in the CAMEO series, we found a higher recanalization rate (36%) in the large and giant aneurysms. This was most apparent in the subgroup of large or giant aneurysms treated without a stent. Importantly, when we combined stenting with Onyx we obtained very durable results in the large and giant aneurysms since only 1 in 25 large/giant aneurysms showed recanalization (4%). This result is very encouraging since no published results with any other device have demonstrated comparable success rates. For example, angiographic occlusion rates for large and giant aneurysms obtained in the ISUIA study by endovascular treatment were poorer and did not approach our 64% occlusion rate at 1 year.

During the evolution of our technique, in the large or giant aneurysms in which we could not use a stent adjunctively, we were aggressive in attempting reconstruction of the parent artery at the aneurysm neck (Fig. 2) to achieve complete and durable occlusion and to reduce the

risk of aneurysm regrowth. However, even after such reconstruction of the parent artery achieved with Onyx, aneurysm regrowth was still observed in wide-necked large and giant aneurysms (69%) necessitating further treatment (Fig. 6). This emphasizes the need for complete parent artery reconstruction, which is apparently not possible without stenting no matter how extensively we reconstruct the neck with the material (Fig. 6).

Although the reason for such recurrence is not clear, we consider that stenting is mandatory to create a complete parent artery reconstruction in the large or giant aneurysms, and we believe Onyx is best used in combination with a stent to obtain durable results. Therefore, stent devices that are suitable for intracranial use are essential in that group. Among the group of aneurysms (25 aneurysms) treated with the Onyx and stent combination, all were balloon-expandable stents that were available for use in the intracranial circulation which limited their use. There have been significant improvements in stent technology in recent years, and new flexible, self-expanding stents that can be delivered via a microcatheter are becoming more widely used [14, 15]. An unresolved issue is that these stents have a very low radial force which may not allow complete reconstruction of the diseased and missing parent artery wall.

Although we observed no rebleeding or delayed bleeding caused by any of the recurrent aneurysms in our series, the risk of a delayed hemorrhage, particularly in patients with large or giant aneurysms treated with coils, is not insignificant in the literature. Of the 12 delayed re-bleeds reported in the series by Murayama et al., 10 occurred in patients with large or giant aneurysms, emphasizing the need to ensure satisfactory angiographic occlusion in this patient group, where possible [11].

The CAMEO series noted a significant number of cases of spontaneous parent artery occlusion [4]. This was particularly an issue in early cases in the series when there was a significant reconstruction of the parent artery by the Onyx with no postprocedural antiplatelet drug regimen administered. During this early period, we also had two delayed asymptomatic parent artery occlusions. However, since that time, our patients have been treated with the clopidogrel and aspirin combination for 6 months and aspirin for life. Since initiation of this regimen, there have been no delayed parent artery occlusions in our series. It is also possible that an extensive healing reaction may be slowly developing in the parent artery that might be responsible for these occlusions, especially in cases where the material was used for crescent-like reconstruction of the parent artery.

Another important issue to be considered is the impact of the treatment on mass effect and related neurological symptoms. Cranial nerve palsy, either oculomotor palsies or optic nerve compression, is the most common symptom of mass effect associated with intracranial aneurysms. Concerns arise when the mass of an aneurysm is replaced with a material which does not shrink significantly and, therefore, the risk that symptoms do not resolve may remain. However, we observed that the majority of the patients (86%) with second and third nerve palsies had complete or significant recovery of function at 12 months or later. Only 2 patients in the group of 21 (9.5%) had symptoms which worsened and which persisted long term. Although it is still not possible definitely to quantify the effect on headache, the headache had resolved or significantly improved in the majority of the patients at discharge (79%) and in nearly all of the patients at follow-up (98%).

The primary technical challenge in the use of Onyx in aneurysms is placement of the remodeling balloon over and beyond the aneurysm neck. This challenge might be more striking when the aneurysm neck is very wide and located at a vessel curve, namely at the ophthalmic artery origin. In a number of cases, catheterization beyond the aneurysm was performed with a regular preshaped microcatheter, and a 0.014–0.016 inch guidewire enabled the necessary 0.010 inch exchange wire to be placed beyond the aneurysm to achieve satisfactory balloon positioning. A 0.014 inch high-torque Syncro wire (Boston Scientific/Target, Freemont, Calif.) and a 0.016 inch hydrophilic gold tip Terumo wire (Terumo, Japan) especially with double curved tip shape, were found very useful to catheterize distally beyond the aneurysm neck. Hyperglide balloons, the later generation of the balloon catheter, are also more suitable for distal navigation over the aneurysm neck.

The introduction of the “Quick Stop” syringe, which permitted immediate stoppage of material flow, improved the technique and offered more safety. This device enables immediate decompression of the built-up pressure in the microcatheter, stopping material as soon as the pressure is released. In the authors’ experience, these improvements in the materials have enhanced the performance of the device in clinical use.

In conclusion, these prospective data on the clinical and angiographic outcomes of this technique show that Onyx can produce durable aneurysm occlusion. This treatment provides more stable results than any other treatment option in the large/giant aneurysms treated with the stent–Onyx combination and in the small aneurysms with only balloon–Onyx. However, further improvements in stent technology may still contribute to increasing the overall success rate in the group of large and giant internal carotid artery aneurysms in the future.

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