Endovascular treatment of complex cerebral aneurysms with onyx hd-500® in 38 patients

OBJECTIVE. — To report our experience with Onyx HD-500® (Micro Therapeutics, Inc., Irvine, CA, USA) in the endovascular treatment of complex intracranial aneurysms as an alternative to treatment with platinum coils.

Patients and Methods. — Between October 2003 and December 2007, 38 patients (20 female and 18 male) were selected for inclusion in the study based on aneurysm size and dome-to-neck ratio. Altogether, 37 (97.3%) aneurysms were located in the anterior circulation, and one (2.7%) was in the posterior circulation. Of these, 35 (92.1%) had wide necks (> 4 mm and/or a dome-to-neck ratio < 2). Clinical and angiographic follow-ups were performed at six and 12 months.

RESULTS. — Successful embolization was achieved in 36 of the 38 patients. Complete occlusion was seen in 29 patients (80.5%), and seven (19.4%) had subtotal occlusion on the immediate angiographic control. After six months, 29 patients (80.5%) initially with total occlusion were stable, while four with subtotal occlusion had progressed to total occlusion and three showed recanalization. Of the latter, two were reembolized and the third patient did not return for retreatment. The one-year angiographic follow-up showed no changes. The morbidity rate was 8.3% (3/36) and procedural mortality was 0%.

CONCLUSION. — The Onyx HD-500 liquid embolic system is a feasible and safe therapeutic option for patients presenting with complex aneurysms, but who are not candidates for other techniques or in whom previous treatment has failed.

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and, more recently, of interventional neuroradiology. Results have been linked to the development of increasingly sophisticated diagnostic and therapeutic technologies, and endovascular techniques have shown lower rates of morbidity and mortality than does classical surgery [1].

Endovascular treatment of cerebral aneurysms has witnessed an explosive advance with the incorporation of new techniques, materials and methods that allow embolization of aneurysms previously considered unsuitable for percutaneous treatment.

Since the time of the first results for endovascular treatment of intracranial aneurysms with Guglielmi detachable coils (GDC) were published, it has been observed that factors such as a wide neck (diameter > 4 mm), dome-to-neck ratio less than 2, intra-aneurysm thrombus, aneurysm size (large and giant), low coil packing density and treatment in the acute phase are related to a higher rate of incomplete occlusion and recanalization [2—4].

Two principal conditions impede conventional endovascular treatment of aneurysms:

- aneurysms with complex radioanatomy, which are not susceptible to treatment with coils, even after balloon remodeling;
- high recanalization rates, mainly with large and wide-necked aneurysms, which may occur 60–80% of the time [5].

Onyx (micro therapeutics, Inc., Irvine, CA, USA), a liquid embolic agent designed for endovascular treatment, is an ethylene-vinyl alcohol copolymer dissolved in the organic solvent dimethyl sulfoxide (DMSO). It was first used for aneurysm treatment in 1999 [6] and, since then, it has evolved into its current version. The clinical results of treatment with Onyx have been published in several studies, but only one prospective, randomized multicenter study [7] showed a lower rate of recanalization and greater aneurysm occlusion stability, mostly in large and gigantic aneurysms, compared with coil treatment alone. The properties of Onyx counteract three major difficulties encountered in the treatment of wide-neck aneurysms with platinum coils alone:

- it produces total or near-total filling of the aneurysm sac;
- it allows excellent aneurysm neck and parent vessel reconstruction (using the balloon remodeling technique);
- it induces a stronger aneurysm neck neendothelization reaction compared with regular platinum coils [4,8,9].

The present report describes our experience with the use of Onyx HD-500® in 38 patients treated at a university hospital center. The patients had intracranial aneurysms that, in the majority of cases, presented radioanatomical difficulties due to aneurysm morphology, size or dome-to-neck ratios less than 2.

Patients and methods

This is a descriptive study of a consecutive series of patients treated between October 2003 and December 2007. The patients were treated with Onyx HD-500 by the senior author (JTC) at the Hospital Clínico, Pontificia Universidad Católica de Chile. All 38 patients had cerebral aneurysms that, considering their physical characteristics (size, location, neck-to-dome ratio < 2), were good candidates for embolization with Onyx HD-500 (Table 1).

Patient selection

Over the study period, 220 patients with cerebral aneurysms were treated with endovascular therapy at our department. Of these, 38 patients (23%) were selected for treatment with Onyx HD-500 because they presented with:

- lateral aneurysms with a dome-to-neck ratio less than 2 and a multilobulated shape;
- aneurysms with a less than 2 dome-to-neck ratio for which treatment with coils, including the balloon remodeling technique, had failed [7];
- wide-necked aneurysms in which the parent vessel did not allow placement of a stent as a therapeutic option;
- large aneurysms (10–25 mm) for which, given the vessel and blood inflow characteristics, short-term rechanneling was highly likely;
- giant aneurysms that did not permit the occlusion test;

<table>
<thead>
<tr>
<th>Location</th>
<th>N&lt;10 mm</th>
<th>N10–24 mm</th>
<th>N&gt;25 mm</th>
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<tr>
<td></td>
<td>DNR&gt;2</td>
<td>DNR&lt;2</td>
<td>DNR&gt;2</td>
</tr>
<tr>
<td>Petrous</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>IC</td>
<td>8</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>C—O</td>
<td>16</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Sup Hyp</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>PComA</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>PICA</td>
<td>1</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>11</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 1: Aneurysm location, size and dome-to-neck ratio (DNR).

IC: intracavernous internal carotid artery; C—O: internal carotid–ophthalmic artery junction; Sup Hyp: superior hypophyseal artery; PComA: posterior communicating artery; PICA: posterior inferior cerebellar artery.
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... systemically recorded for better characterization of the aneurysms and treatment planning.

Anticoagulation and antiplatelet medications

All procedures were performed under general anesthesia. Systemic heparinization was started with 5000 U of heparin bolus, with an additional 500–1000 U/h to keep the activated clotting time (ACT) within twice the value of the baseline ACT. For patients with acute SAH, clopidogrel was administered via a nasogastric probe on the same day as the procedure. The remaining patients were all started on daily oral administration of 300 mg of clopidogrel and 325 mg of aspirin for at least three days prior to the procedure. After the procedure, only low-molecular-weight heparin was administered. Clopidogrel was maintained for six months, and aspirin was continued for one-year (Plavix® 75 mg/day and aspirin 325 mg/day orally).

Embolization procedure with Onyx HD-500

A bilateral femoral puncture, by the Seldinger technique, was used for endovascular access. Using an ENVOY 5-F guiding catheter (Cordis Corp., Miami Lakes, FL, USA), a HiperGlide™ Balloon (Micro Therapeutics, Inc.) was inserted (15 mm, 20 mm or 30 mm, depending on the characteristics of the vessel and the aneurysm) into the parent artery in front of the aneurysm neck. With a second (6-F) guiding catheter, a Rebar™ 14 Micro Catheter (Micro Therapeutics, Inc.) was placed in the lumen of the aneurysm. The correct placement and size of the balloon were tested by injecting contrast media into the aneurysm with an inflated balloon retained in the lumen—the so-called occlusion test. After filling the dead space of the microcatheter with 0.2 mL of DMSO, the Onyx HD-500 was injected at a rate of 0.1 mL/min, using a precision syringe, with the balloon inflated. Injection lasted a maximum of three minutes, after which the balloon was deflated for two minutes. This procedure was repeated with new injections of Onyx HD-500 until complete occlusion of the aneurysm was achieved.

When the embolic material makes contact with an aqueous solution, it forms a polymeric sponge called a "cast", which initially has a semi-liquid center. When the material is injected into the interior of the cast, it grows progressively, eventually occupying all of the available space. The quantity used varies according to the size of the aneurysm. After 10 minutes (the time required for Onyx HD-500 to completely solidify), the microcatheter is removed with the balloon deflated.

In some patients, only one femoral access is used for a 6-F guiding catheter (ENVOY, Cordis Corp., internal lumen: 1.8 mm), through which both the balloon and the microcatheter are introduced.

In three (8.3%) patients with recanalization highly likely due to radioanatomical features, coils (ev3, Irving, CA, USA) were placed prior to the Onyx HD-500 injection.

Results

Of the 38 patients, embolization was achieved in 36 (94.7%) cases (Figs. 1–3). In two patients (who had one large and one giant aneurysm, respectively), marked arterial dysplasia did not allow for positioning of the balloon, which meant that the occlusion test to secure embolization could not be performed. Thus, the treatment-failure rate was 5.3% (2/38). The angiographic results are summarized in Table 3.

Complete occlusion was achieved in 29 (80.5%) of the 36 aneurysms (Table 3). In seven (19.4%) cases, the occlusion was subtotal on the immediate angiographic control. At the sixth and 12-month angiographic follow-ups, these

Table 2 Clinical characteristics of the studied aneurysms.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>n</th>
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<tbody>
<tr>
<td>Incidental</td>
<td>17</td>
</tr>
<tr>
<td>Mass effect</td>
<td>10</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>8</td>
</tr>
<tr>
<td>Post-coiling recanalization</td>
<td>1</td>
</tr>
<tr>
<td>Growth</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
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</table>

* Patients initially embolized with Onyx HD-500
29 patients who had initially achieved total occlusion were stable. Of the seven aneurysms with subtotal occlusion, four progressed to total occlusion, and three to partial occlusion with significant recanalization, at the six-month angiographic follow-up.

Recanalization was seen in three (8.3%) of the 36 aneurysms. Two of these (one large and one giant aneurysm, respectively) were retreated with Onyx HD-500, which led to post-interventional total occlusion that remained stable at six and 12 months. The third patient did not return for retreatment after the angiographic control. The two retreated patients had been embolized with coils and Onyx HD-500 initially. However, due to distortion of the parent vessel in one patient, placement of the balloon and microcatheter was difficult, with marked spasm of the internal carotid artery (ICA) during Onyx injection. Complete occlusion and total remodeling of the carotid siphon was achieved, but the post-procedural neurological status showed clinical deterioration due to cortical infarcts in the medial cerebral artery (MCA) territory, with clinical improvement at the six-month follow-up. On angiographic examination at 12 months, total stability in the occlusion of all patients had been achieved.

No progression of mass effect was observed after Onyx treatment in the 10 patients with preoperative mass effects. In fact, at the clinical follow-up, regression of the mass effect was observed in all cases.

However, clinical complications and unfavorable anatomical changes were seen in three patients. One was a case of clinical ischemic complication with moderate permanent deficit due to prolonged balloon occlusion time because of a complicated dysplastic artery. This patient had a modified Rankin scale (mRS) score of 3 at four months and 3 at six months. Two other patients presented with no clinical complications, although intimal hyperplasia adjacent to the aneurysm neck was observed. Of these two cases, the process was reversible with no clinical consequences in one patient at the 12-month follow-up. The other patient progressed to occlusion of the artery, compensated for by the Circle of Willis, and showed no clinical complications on angiographic examination at six months.

The eight patients with ruptured aneurysms presented with no complications during the procedure and, instead, showed favorable clinical changes. Post-procedural cranial nerve paralysis mass effect was not observed. The morbidity rate was 1/36 (2.8%) and the procedural mortality was 0%.

**Discussion**

**Feasibility of Onyx treatment**

The objective of treatment is complete occlusion, as partial occlusion is associated with rebleeding with endovascular and surgical treatments. Of these two options, rebleeding is more frequent with endovascular treatment, although the difference is not statistically significant [10]. In 2002, Mawad et al. [11] introduced the clinical use of Onyx by successfully treating large and giant intracranial aneurysms and, in 2004, Molyneux et al. [8] reported the results of a multicenter evaluation using Onyx for embolization of intracranial aneurysms. After 12 months, more than 90% total or subtotal occlusion was achieved, with morbidity and mortality rates comparable to those with other endovascular techniques for similar clinical conditions. The present results with Onyx were from the embolization of 36 wide-neck aneurysms in 38 patients, and are comparable to the current standards of clinical practice in the endovascular management of intracranial saccular aneurysms. Indeed, our study shows that selective embolization of intracranial aneurysms with a liquid embolic system is feasible and effective in a selected population.

**Anatomical results with Onyx**

In the first multicenter study [8] of Onyx embolization of intracranial aneurysms, 97 patients with 100 aneurysms were treated. In that study, 80% of the aneurysms were large or giant and remained stable one-year after embolization. Furthermore, at the one-year follow-up, there was complete occlusion in 93% of the small aneurysms, 77% of the large aneurysms and 57% of the giant aneurysms, with an overall aneurysm occlusion rate of 79%. Retreatment was necessary in only 10% of patients.

In 2005, Lubicz et al. [12] reported on a series on 41 aneurysms treated with Onyx that included 30 large or giant

<table>
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<th>Table 3</th>
<th>Immediate and late-result angiography of all aneurysms by size.</th>
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<td>Angiographic result</td>
<td>&lt; 10 mm</td>
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<tr>
<td>Immediate post-embolization</td>
<td>n = 10</td>
</tr>
<tr>
<td>Complete</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Incomplete</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Control at six month</td>
<td>n = 10</td>
</tr>
<tr>
<td>Complete</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Incomplete</td>
<td>0</td>
</tr>
<tr>
<td>Recanalization</td>
<td>0</td>
</tr>
<tr>
<td>Control at 12-month</td>
<td>n = 10</td>
</tr>
<tr>
<td>Complete</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Incomplete</td>
<td>0</td>
</tr>
<tr>
<td>Recanalization</td>
<td>0</td>
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*One patient did not return for retreatment after the first angiographic control.*
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Figure 1  Selective left internal carotid artery (ICA) lateral angiogram. A, B: shows a large aneurysm of the ICA—posterior communicating artery with a posterior orientation; C: unmasked fluoroscopic lateral view shows radiopaque Onyx HD-500® filling the lumen of the aneurysm; D, E: post-procedural control angiography shows total occlusion of the aneurysm.

aneurysms, in which intracranial stents had been used in 15 cases. Of the large and giant aneurysms, there was complete occlusion in 63% and 57%, respectively, on follow-up. There was recanalization of nine aneurysms (32%), all of which were large or giant and partially thrombosed. Retreatment was necessary in 10% of patients.

The largest series involving Onyx embolization of intracranial aneurysms was by Cerkige et al. in 2006 [13]. The authors treated 100 aneurysms with Onyx HD-500 (65 were small, and 35 were large or giant), with angiographic control for up to five years. The results in the large and giant aneurysms emphasize the indication of Onyx for these types of aneurysms due to the lower rate of recanalization compared with endovascular treatment with coils. Recanalization was seen in 12 aneurysms, all of which were large or giant, in which stents had not been used and probably should have been. Immediate aneurysm occlusion occurred in 97% of the small aneurysms, 78% of the large aneurysms and 76% of the giant aneurysms. At the three and six month follow-ups, the rates of complete occlusion were 100% for small, 62% for large and 65% for giant aneurysms.

In 2009, Piske et al. [14] reported their results with Onyx HD-500 for the endovascular treatment of wide-neck intracranial aneurysms with platinum coils, with which there is usually a high rate of incomplete occlusion and recanalization. Complete aneurysm occlusion, however, was seen in 65.5% of aneurysms on the immediate control, in 84.6% at six months and in 90.3% at 18 months. Rates of complete occlusion were 74%, 95.1% and 95.2%, respectively, at these times for small aneurysms, and 53.3%, 70% and 80%, respectively, for large aneurysms. Progression from incomplete to complete occlusion was seen in 68.2% of all aneurysms, with a higher percentage in small aneurysms (90.9%). Aneurysm recanalization was observed in three (4.6%) patients, with retreatment necessary in two (3.3%) patients.

Published data for 3-D Micrus coils (Micrus Endovascular, Sunnyvale, CA, USA) show immediate complete occlusion rates similar to those with regular coils for small aneurysms with small necks, and 70% total occlusion for small aneurysms with large necks [15,16]. With Matrix coils (Boston Scientific), the results ranged from 17% to 68% total occlusion for small aneurysms, the majority of which had small necks [17,18]. In the treatment of small aneurysms with large necks with HydroCoils, Berenstein et al. [19] reported 33% total occlusion, 57% recanalization and 35% progression to complete occlusion.

Intracranial stents have been used in the treatment of aneurysms that allow the placement of coils and reinforcement of vessel walls, and have resulted in delayed stenosis and aneurysm recurrence [20]. The reported rates of complete occlusion range from 8% to 57%, with up to 12% recanalization and retreatment, and technical complications of up to 23.5%, mainly due to thromboembolic events [3,10,19]. In cases of large aneurysms, complete occlusion was seen in only 17.6% of cases [19].
In addition to the use of stents and coils, there are other, new options, such as flow-diverter devices. The long-term effects of reconstruction of vascular walls after thrombosis of the aneurysm sac with these devices represent a different approach to the treatment of aneurysms. While Onyx fills the aneurysm, flow diverters change the direction of flow within the aneurysm sac. However, these devices have not been proven to reduce recanalization rates in intracranial aneurysms, many of which can otherwise be treated with the remodeling technique as the sole treatment. Moreover, the technique has yet to be studied in detail, and larger sample populations and longer follow-up periods are needed. Treatment evaluations should also consider the complications associated with stent placement that are sometimes underestimated or not described in detail.

High recanalization rates remain an unresolved problem [2] with the use of coils for large aneurysms. The results published with this technique reveal that aneurysms with necks more than 4 mm and a dome-to-neck ratio less than 2 (wide-neck aneurysms), as well as large and giant aneurysms, have low rates of complete occlusion and high rates of recanalization. These data have also been confirmed in more recent large series with long follow-up periods, regardless of the type of coil used [15].

Complication rates with Onyx

Permanent morbidity and mortality rates in the first multicenter study [8] for Onyx embolization of 100 intracranial aneurysms were 8% and 2%, respectively. In the Lubicz et al. [12] series of 41 aneurysms, there were four cases of complications (10%) and one death (2.4%). In the Cerkiye et al. [13] series, the overall morbidity was 8% and mortality was 3.2% while, in the Piske et al. [14] series, procedural mortality was 2.9% and overall morbidity was 7.2%.

Of the present study patients, 36 of the 38 had wide-necked aneurysms, and 26 had large or giant lesions. Overall, the patients represented highly complex cases where embolization with coils would have been difficult or unstable over time. Thus, in our opinion, the 8.3% (3/36) recanalization rate is low. Where recanalization did occur, it was due to growth of the aneurysms, and was resolved by a second embolization in two of the three patients. At the six-month angiographic follow-up, four aneurysms with angiographically subtotal occlusions had progressed to total occlusions.

It has been demonstrated that Onyx can produce durable aneurysm occlusion in patients with difficult, large and giant wide-neck intracranial aneurysms, cases where other...
endovascular techniques are likely to fail and surgery carries substantial morbidity. However, endothelial hyperplasia with ICA stenosis can occur and may be related to Onyx embolization. In the present study, there were two cases of endothelial hyperplasia that, in one case, progressed to complete occlusion at follow-up.

Figure 3  Selective left ICA angiogram. A: oblique view shows a giant aneurysm in the ICA supraclinoid segment with a posterolateral orientation; B: angiography shows coils partially filling the end of the aneurysm sac; C: angiography shows balloon placement occluding the neck of aneurysm; D: unmasked fluoroscopic lateral view shows radiopaque Onyx HD-500 filling the lumen of the aneurysm; E, F: post-procedural anteroposterior and lateral angiograms demonstrate progression and complete occlusion of the aneurysm sac.

Indications for Onyx

The use of liquid embolic agents is an alternative for selected cerebral aneurysms, although the procedure requires sufficient expertise. The current principal indication for Onyx HD-500 is lateral aneurysms with wide necks, and cases where surgery comes with high risks [8]. Considering that many of these patients are considered untreatable by surgical and/or classical endovascular methods, we believe that the results with Onyx are optimal. Onyx has been proven to be an effective therapeutic tool, and recent studies [13,21] show that it is ethically correct to offer this treatment to carefully selected patients.

Our present results are similar to those of other series and are due to the appropriate selection of patients. The benefits of this new technique are clear for large and giant aneurysms and/or aneurysms with wide necks. In such cases, the morbidity and mortality rates were better than those associated with surgical clipping. However, the approach remains technically challenging, and should not be proposed as a first-line therapeutic option for small aneurysms, in which coil embolization has been proven safe and efficacious.

Conclusion

Onyx liquid embolization of intracranial complex aneurysms is safe and effective, with morbidity and mortality rates similar to those with other currently used endovascular techniques. Our present results show excellent occlusion rates for wide-neck, small and large aneurysms, suggesting that Onyx embolization is a useful alternative in cases of aneurysms that are difficult to treat with other techniques.

Disclosure of interest

The authors declare that they have no conflict of interest concerning this article.
References