Preliminary Experience of Cerecyte Coils in the Treatment of Intracranial Aneurysms

M. LEONARDI, M. DALL'OLIO, O. ORTIZ VASQUEZ, C. QUERCETTI

Neuroradiology Department, Bellaria Hospital, University of Bologna; Bologna, Italy

Key words: brain aneurysms, endovascular treatment, active coils

Summary

Coil embolization of intracranial aneurysms is the first choice treatment in many centres worldwide. The ISAT study reported in favour of endovascular treatment even though coil embolization carries a higher risk of revascularization than surgical clipping. Bioactive coils boosting fibrosis within the aneurysm and neointimal production could counteract the tendency of embolized aneurysms to re-open. We reviewed our cohort in a retrospective study based on the following inclusion criteria: 1) Cerecyte coils (Micrus Endovascular, San Jose, Calif) were the only bioactive coils deployed. 2) Cerecyte coils were used in the first embolization procedure.

Between July 2005 and December 2007 39 patients matched these inclusion criteria, 15 men and 24 women (average age 63.5 years) with 44 aneurysms. Treatment outcomes were: 30 aneurysms completed excluded from the circulation, 13 aneurysms almost completed excluded from the circulation, one incomplete aneurysm occlusion. Two aneurysms out of 44 recurred during follow-up (4.54%) and were re-embolized.

The radio-opacity and conformational memory of the Cerecyte coils were satisfactory and they were easy to manoeuvre and detach.

Introduction

Coil embolization of intracranial aneurysms is the first choice treatment in many centres worldwide. Since publication of the results of the International Subarachnoid Aneurysm Trial (ISAT) ruptured aneurysms tend to be treated

by endovascular procedures rather than neurosurgery⁷. Subsequent trials demonstrated a reduced mortality and morbidity at one year in patients treated with coils as opposed to surgery^{11,18}. The weak point of embolization is the frequency of aneurysm recurrence after endovascular treatment varying from 14 to 54%^{4,5,11,12,16,18,19}. This wide variation in the percentage of revascularization depends on the size of the aneurysm and whether embolization resulted in complete or incomplete aneurysm occlusion. Recurrence is more likely in the case of giant aneurysms associated with wall thrombosis, or when exclusion of the lesion from the circulation was incomplete^{5,12}.

Aneurysm revascularization increases the risk of bleeding. Different coils have been devised to counteract late aneurysm recurrence, including biologically modified devices^{6,9,13-15}. The bioactive material used to produce Cerecyte coils (Micrus Endovascular, San Jose, CA, USA) is the monomer, polyglycolic acid.

This study describes the preliminary experience of the Neuroradiology Service at Bellaria Hospital, Bologna, using bioactive Cerecyte coils to embolize ruptured and unruptured intracranial aneurysms.

Materials and Methods

Cerecyte coils are made of platinum incorporating a strand of the monomer polyglycolic acid within the lumen of the three-dimensional microcoil. The polyglycolic acid is then degraded by hydrolysis when placed in contact with the water molecules contained in blood.

Figure 1 Diagnostic angiography, anteroposterior (A) and lateral (B) views showing an aneurysm of the anterior communicating artery.

Technique: We inserted a 5F guiding catheter (Envoy, Cordis) coaxially into the internal carotid or vertebral artery then coaxially advanced a microcatheter (Excell 14 or Excelsior 10, Boston Scientific) through a 0.014" microguide (Synchro 14, Boston Scientific) to reach the base of the aneurysm for coil deployment. All procedures were carried out using an Advantx biplane angiographic system (General Electric) with patients under general anaesthesia.

We retrospectively selected 39 patients, 15 men and 24 women (average age 63.5 years) with 44 aneurysms treated between July 2005 and December 2007. The following inclusion criteria were adopted:

- 1) Cerecyte coils were the only bioactive coils deployed.
- 2) Cerecyte coils were used in the first embolization procedure.

The study included wide-necked aneurysms treated with intracranial stents and coils divided into the following sizes:

- 1) Maximum diameter < 1 cm.
- 2) Maximum diameter between 1 and 2.5 cm (large).
- 3) Maximum diameter > 2.5 cm (giant).

MR angiography (TOF angiographic sequences) was used for follow-up after treatment. Control angiography and further embolization were only performed if there was MR evidence of revascularization of the embolized aneurysm.

Medical management associated with endovascular treatment: To avoid the onset of peri-procedural or long-term ischaemic events, all patients received anticoagulant and anti-aggregant therapy according to the following protocol. After inserting the guiding catheter into the internal carotid or vertebral artery i.v. heparin was administered to obtain coagulation times between 250 and 350 seconds with 1g lysine acetylsalicylate (Aspegic) bolus injection. These doses were reduced or delayed after deploying the first coils in acute cases. During the 48h after the procedure patients were given low molecular weight heparin (Clexane) 4000 X 2, ticlopidine (Tiklid) 250 mg X 2, acetylsalicylic acid (Ascriptin) 0.3 g X 1, and ranitidine (Zantac) 150 mg 1 tablet daily.

Anti-aggregant therapy was continued at these doses for a week after endovascular treatment. Thereafter ticlopidine (Tiklid) was reduced to 250 mg once daily in association with the other drugs for another week. Ticlopidine was then suspended, whereas acetylsalicylic acid (Ascriptin) 0.3 g X and ranitidine (Zantac) 150 mg 1 tablet daily were continued for a further two weeks or six months if an intracranial stent had been deployed with the coils. Haemochrome was measured after ten days of treatment to disclose any reduction in platelet count. Clopidogrel bisulphate (Plavix) is only available on the National Health Service in Italy for heart disease patients. Whenever possible, especially after intracranial stent

Figure 2 Angiography, anteroposterior (A) and lateral (B) views. Final control after embolization showing the aneurysm completely excluded from the circulation.

placement, clopidogrel bisulphate can be replaced by ticlopidine (Tiklid) at a dose of 75 mg daily at the patient's expense.

Results

The following lesions were treated:

- 30 aneurysms with a maximum diameter <1 cm;
- nine aneurysms with a maximum diameter between 1 and 2.5 cm;
- five aneurysms with a maximum diameter > 2.5 cm.

Seven intracranial stents were deployed:

- six Neuroform (Boston Scientific);
- one Leo (Balt).

Cerecyte coils alone were deployed in 15 aneurysms.

In all, 21 patients with 24 unruptured aneurysms were treated electively, whereas 18 patients with 20 aneurysms presented with subarachnoid hemorrhage caused by a ruptured aneurysm and were treated in an emergency setting.

Among the 21 patients with 24 unruptured aneurysms, 95-100% occlusion was obtained in 20 cases; 95% occlusion signifies minimum patency at the base of the aneurysm neck which may be impossible to exclude completely. Follow-up examinations confirmed stable occlusion in 19 patients, four of whom had been treated by placement of a Neuroform stent to

Figure 3 MR angiography, follow-up with TOF sequences (A-C) 23 months after embolization confirming exclusion of the aneurysm from the circulation.

Figure 4 Diagnostic angiography, anteroposterior (A) and lateral (B) views showing an aneurysm of the anterior communicating artery.

protect the aneurysm neck. A further four aneurysms were incompletely excluded from the circulation, two associated with insertion of Neuroform stents and one with placement of a Leo stent. These four lesions included a large aneurysm of the carotid siphon, one aneurysm on the vertebral artery, one on the anterior communicating artery and one on the pericallosal artery. Occlusion was confined to 80-90% in these cases to avoid creating mass effect on the stents and to keep patent the origin of the anterior cerebral and pericallosal arteries treated without stent deployment. Around 80% oc-

clusion was achieved, remaining stable at subsequent follow-up controls. Occlusion of the aneurysmal cavity increased from 80 to 95% and from 90 to 95% in four cases and from 95 to 100% in two cases. Complete occlusion was only obtained in one patient with a large vertebral artery aneurysm at the origin of the left postero-inferior cerebellar artery during a second embolization procedure six months after the first which had resulted in incomplete but stable aneurysm occlusion.

Among the 18 patients with 20 aneurysms presenting with subarachnoid hemorrhage, al-

Figure 5 MR angiography, anteroposterior (A) and lateral (B) views. Final control after embolization showing the aneurysm completely excluded from the circulation.

most complete occlusion (95-100%) was obtained in 17, and 80-90% occlusion in three. Outcome was stable at follow-up in all cases. A favourable change in occlusion occurred at follow-up examination in four patients with an initial occlusion of 70% increasing to 90% in one case, from 80% to 100% in two and from 90% to 100% in one. One large aneurysm of the anterior communicating artery required two embolization procedures to obtain complete occlusion due to re-opening of the aneurysm cavity caused by changes in the wall of the lesion rather than coil compaction following treatment.

All the Cerecyte coils were correctly positioned without complication either during deployment within the aneurysm or when the coils were detached.

Two aneurysms out of 44 recurred during follow-up (4.54%). One was a large aneurysm located on the left vertebral artery above the origin of the postero-inferior cerebellar artery, the other was an aneurysm on the anterior communicating artery. After diagnostic angiography both of these aneurysms were embolized for a second time using Cerecyte and GDC coils. Complete exclusion of the aneurysms was obtained in both cases and confirmed at follow-up MR angiography six months after the procedure for the vertebral artery lesion and one month after for the anterior communicating artery aneurysm.

MR angiography follow-up in the remaining patients at the following times failed to disclose aneurysm recurrence:

- within three months in 14 patients;
- between three and 12 months in 17 patients (figures 1-3);
- between 12 and 24 months in two patients;
- six patients failed to present at follow-up.

Discussion

Embolization is the first choice treatment for ruptured and unruptured intracranial aneurysms whenever anatomically feasible for two main reasons: the treatment has been proved to be effective and is less invasive than surgery.

The results of the International Subarachnoid Aneurysm Trial (ISAT), first published in October 2002¹⁰, demonstrated lower rates of morbidity and mortality at one year after in patients treated by endovascular embolization as opposed to surgery^{11,18}. In addition the trial re-

Figure 6 MR angiography, follow-up with TOF sequences (A,B) 3 months after embolization showing partial revascularization of the aneurysm.

ported a low risk of rebleeding of all aneurysms treated, but coil embolization carried a higher risk of aneurysm recurrence than surgical clipping. A further review of ISAT published in 2005¹¹ confirmed the initial findings extending the reduced mortality and morbidity of patients after embolization to more than seven years. It also reported a greater risk of epilepsy in patients who underwent surgery. Endovascular treatment is much less invasive than surgery and the ongoing improvements and reduced calibre of materials allow superselective navigation thereby minimizing the risks of vessel

Figure 7 Diagnostic angiography, anteroposterior (A) and lateral (B) views before treatment confirming MR angiography evidence of an aneurysm of the anterior communicating artery.

occlusion and damage to the arterial walls. However, the long-term outcome of endovascular treatment appears to be less reliable than that of surgery. ISAT and other studies have reported widely different rates of aneurysm recurrence after embolization varying from 14 to 54%^{4,5,11,12,16,18,19}. This wide variation in the percentage of revascularization depends on the size of the aneurysm, whether embolization resulted in complete or incomplete aneurysm occlusion and whether treatment was performed in an emergency setting or not.

Large aneurysms (>1 cm) and to a greater extent giant aneurysms (>2.5 cm) are more likely to recur, especially when the aneurysms arise in a terminal position (e.g. basilar apex). Coils tend to migrate within the thrombotic material resulting in revascularization. Acute aneurysms cannot always be embolized completely even when angiographic control at the end of the procedure appears to show complete occlusion. This is because subarachnoid hemorrhage can "contract" the subarachnoid space thereby shrinking the aneurysm which subsequently re-expands when the blood has been resorbed leading to coil compaction. For these reasons surgeons are inclined to consider young patients surgical candidates and elderly patients mainly suited to neuroradiological management. This tendency is, however, contradicted both by the ISAT findings on mortality rates and peri-operative risk in ruptured aneurysms after endovascular treatment and

the fact that embolization is less invasive even when two separate treatment sessions are required. In addition, the long-term risk of recurrence of embolized aneurysms is low, from 0.2 to 0.32% per patient per year^{11,20}.

Patient choice is involved when aneurysms are suitable for treatment by either neurosurgery or interventional neuroradiology. Because the experts may disagree, patients must be made aware of treatment procedures and outcomes to be in a position to make an informed decision on which option to choose.

Several different coils have been devised to counteract aneurysm recurrence. Hydrophilic coils increase the volume of the embolizing materials²; other coils have been coated with radioactive or bioactive materials. Animal studies on the new biologically active coils showed enhanced fibrotic formation within the aneurysm and stimulated neointimal production which should eliminate or in any case reduce the frequency of aneurysm recurrence after embolization¹³. We mainly use Cerecyte coils because they incorporate the monomeric form of polyglycolic acid as a bioactive material. As this substance has a half-life of around five months, it triggers a mild but prolonged inflammatory tissue reaction, thereby reducing the risk of arterial thrombosis. The polyglycolic acid strand is incorporated within the lumen of the microcoil so that Cerecyte and Micrus bare platinum coils can be manoeuvred and detached in the same way^{3,8}. Cerecyte coils do not need to be used

Figure 8 Angiography, anteroposterior (A) and lateral (B) views. Final control after the second embolization showing the aneurysm completely excluded from the circulation.

alone to increase occlusion capacity. One or two Cerecyte coils deployed at the outset are sufficient to create an anchoring scaffold for the coil mesh to facilitate the embolization of wide-necked aneurysms as shown in our study on Micrus coils⁸. The aneurysm can then be filled with any type of coil depending on operator preference and the size and shape of the aneurysmal cavity. Our inclusion criteria were confined to Cerecyte coils as the only bioactive devices used and the deployment of Cerecyte coils in the first embolization procedure. This excluded cases in which fibrosis within the aneurysm and neointimal production was already underway to minimize the number of variables and make the in-

terpretation of results more reliable. Only two aneurysms recurred in our series (4.54%) and both were large lesions which in general have a higher rate of revascularization. A second embolization procedure completely excluded the aneurysms without complications, further demonstrating the minimal invasivity of the procedure given the complexity and severity of these lesions. Our follow-up findings using MR angiography showed that endovascular treatment proved stable even when aneurysm occlusion was incomplete. As we believe the invasiveness of a diagnostic test should be proportional to the likelihood of subsequent treatment, angiography is only performed at our in-

Figure 9 MR angiography, follow-up with TOF sequences (A-C) 1 month after the second embolization confirming exclusion of the aneurysm from the circulation.

stitution if MR angiography discloses evidence of aneurysm recurrence. Our long-standing experience with this type of follow-up has shown that small leaks of contrast medium into an aneurysm can also be identified on TOF sequences using high field strength MR systems (figures 4-9).

Conclusions

Our 20 months retrospective study selecting 46 aneurysms embolized with Cerecyte coils shows that the new devices can be reliably used in routine clinical practice and constitute a fur-

ther advance in the material available for the endovascular treatment of intracranial aneurysms. Two main conclusions emerge from the study:

1. Incorporating a bioactive polymer into a coil does not reduce its radiological opacity or change its manoeuvrability or shape memory which are among the prime features of Micrus coils in general.

2. Cerecyte coils do not need to be used alone to increase occlusion capacity. One or two Cerecyte coils deployed at the outset are sufficient to create an anchoring scaffold for the coil mesh within the aneurysm, and to stimulate the fibrous occlusion of the aneurysm.

References

- 1 Abrahams IM, Forman MS et Al: Delivery of human vascular endothelial growth factor with platinum coils enhances wall thickening and coil impregnation in a rat aneurysm model. *Am J Neuroradiol* 22: 1410-1417, 2001.
- 2 Arthur AS, Wilson SA et Al: Hydrogel-coated coils for the treatment of cerebral aneurysms: preliminary results. *Neurosurg Focus* 18:E1, 2005.
- 3 Butteriss D, Gholkar A et Al: Single-Center Experience of Cerecyte coils in the Treatment of Intracranial Aneurysms: Initial Experience and Early Follow-Up Results. *Am J Neuroradiol* 29: 1-4, 2008.
- 4 Byrne JV, Sohn MJ, Molyneaux AJ: Five year experience in using coil embolization for ruptured intracranial aneurysms: outcome and incidence of late rebleeding. *J Neurosurg* 90: 656-663, 1999.
- 5 Friedman JA, Nichols DA et Al: Guglielmi detachable coil treatment of ruptured saccular cerebral aneurysms: retrospective review of a 10-year single-center experience. *Am J Neuroradiol* 24: 526-533, 2003.
- 6 Kallmes DF, Fujiwara NH et Al: A collagen-based coil for embolization of saccular aneurysms in a new Zealand White rabbit model. *Am J Neuroradiol* 24: 591-596, 2003.
- 7 Leonardi M, Dall'Olio M et Al: Intracranial Stenting in the Treatment of Wide-Necked Aneurysms. *Interventional Neuroradiology* 13: 19-30, 2007.
- 8 Leonardi M, Simonetti L, Cenni P, Raffi L: 3D Micrus Coil "Cage" in Wide-Necked Aneurysms. *Interventional Neuroradiology* 9: 141-152, 2003.
- 9 Marx WE, Cloft HI et Al: Endovascular treatment of experimental aneurysms by use of biologically modified embolic devices: coil-mediated intra-aneurysmal delivery of fibroblast tissue allografts. *Am J Neuroradiol* 22: 323-333, 2001.
- 10 Molyneaux A, Kerr R et Al: International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 360: 1267-1274, 2002.
- 11 Molyneux AJ, Kerr RS et Al: International subarachnoid aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet* 366: 809-817, 2005.
- 12 Murayama Y, Nien YL et Al: Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. *J Neurosurg* 98: 959-966, 2003.
- 13 Murayama Y, Suzuki Y et Al: Development of a biologically active Guglielmi detachable coil for the treatment of cerebral aneurysms. Part 1. In vitro study. *Am J Neuroradiol* 20: 1986-1991, 1999.
- 14 Murayama Y, Tateshima S et Al: Matrix and bioabsorbable polymeric coils accelerate healing of intracranial aneurysms: long-term experimental study. *Stroke* 34: 2031-2037, 2003.
- 15 Murayama Y, Viñuela F et Al: Ion implantation and protein coating of detachable coils for endovascular treatment of cerebral aneurysms: concepts and preliminary results in swine models. *Neurosurgery* 40: 1233-1243, 1997.
- 16 Ng P, Khangure MS et Al: Endovascular treatment of intracranial aneurysms with Guglielmi detachable coils: analysis of midterm angiographic and clinical outcomes. *Stroke* 33: 210-217, 2002.
- 17 Nestor R, Gonzalez, Aman B et Al: Angiographic Evidence of Aneurysm Neck Healing Following Endovascular Treatment with Bioactive Coils. *Am J Neuroradiol* 26: 912-914, 2005.
- 18 Raymond I, Guilbert F et Al: Long-term angiographic recurrence after selective endovascular treatment of aneurysms with detachable platinum coils. *Stroke* 34: 1398-1403, 2003.
- 19 Raymond J, Roy D et Al: Endovascular treatment of acutely ruptured and unruptured aneurysms of the basilar bifurcation. *J Neurosurg* 86: 211-219, 1997.
- 20 Sluzewski M, van Rooij WJ et Al: Late rebleeding of ruptured intracranial aneurysms treated with detachable coils. *Am J Neuroradiol* 26: 2542-2549, 2005.

M. Leonardi, M.D.
Neuroradiology Department
Bellaria Hospital
Via Altura, 3
40139 Bologna, Italy
E-mail: marco.leonardi@centauro.it