Spanish Registry for Embolization of Small Intracranial Aneurysms with Cerecyte Coils (SPAREC) Study* Early Experience and Mid-Term Follow-up Results

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Key words: cerebral aneurysms, embolization, endovascular therapy

Summary

This study aimed to report the results obtained in treating small ruptured and unruptured intracranial aneurysms using Cerecyte coils. A prospective, non-randomized multicenter registry operating in Spain with a reporting period between May 2005 and September 2007. We present clinical and angiographic results for 48 small aneurysms (26 ruptured, five with III cranial nerve paresis, and 17 incidental) that had undergone six months' follow-up. The volumetric percentage occlusion (VPO) achieved and percentage bioactive coils (PBC) used were assessed.

No episodes of bleeding occurred during the follow-up period. The technical complication rate was 10.4% (five cases): four thromboembolic complications resolved with medication (8.3%) and one asymptomatic protrusion of a coil into the parent vessel. The clinical complication rate for the procedure was 2.1% (occlusion of the anterior choroidal artery in a ruptured anterior choroidal aneurysm). Mean VPO was 25.2%. Balloon-assisted technique (BAT) was used in 60.4% of cases. The VPO was higher in the BAT-treated cases ($P < 0.05$). The overall six-

month recanalization rate was 16.7% (12.5% minor and 4.2% major recanalizations). Neck size and VPO were unrelated to the recanalization rate. The PBC was higher in cases with progressive Deployment of the device is safe from the standpoint of periprocedural technical and clinical complications. No episodes of hemorrhage were recorded during follow-up. The six-month recanalization and retreatment rates compared favorably with most endovascular platinum and bioactive coil series.

Introduction

The International Subarachnoid Aneurysm Trial (ISAT)^{1,2,3} demonstrated improved outcomes in patients treated by an endovascular approach compared with patients treated by surgical clipping in terms of survival free of disability at one year. The early survival advantage was maintained for up to seven years and was significant ($P = 0.03$). Retreatment rate was 17.4% in the endovascular group compared with 3.8% in the surgical group, with a low risk of recurrent hemorrhage in both groups.

Several strategies for improving endovascu-

*Disclosure

The SPAREC study was supported by CARDIVA (Madrid, Spain) and Micrus Corporation (Irvine, CA, USA). The authors have no financial interest in the results of this study or any affiliation with the device manufacturer.

lar results are currently being looked at. Most of these involve improving coil technology or achieving better packing and promoting a strong endosaccular healing response. The Cerecyte coil consists of a regular bare platinum coil with polyglycolic acid (PGA) running through the lumen of the primary wind. The primary purpose of the Spanish Registry for Embolization of Small Intracranial Aneurysms with Cerecyte Coils (SPAREC) study is to assess the procedural safety of Cerecyte bioactive coils taking into account periprocedural, clinical, technical, and angiographic complications and to evaluate the angiographic stability of intracranial aneurysms and the clinical outcome at six months. The study was approved by the ethics committee of the coordinating center (Gregorio Marañón Hospital, Madrid, Spain).

Materials and Method

Cerecyte Device

The Cerecyte coil (Micrus Endovascular, San Jose, CA, USA) consists of a regular bare platinum coil with polyglycolic acid (PGA) running through the lumen of the platinum wind which provides stretch resistance during handling. The total volume of platinum is the same as in a standard bare platinum coil.

Patient Population

SPAREC is a non-randomized, prospective, multi-center registry that has been operating in Spain since May 2005. The period reported here is up to September 2007, analyzing the outcomes in 47 patients with 48 small cerebral aneurysms (26 ruptured, five with III cranial nerve paresis, and 17 incidental) treated at various centers and followed for a full six months. The ruptured aneurysms were Hunt-Hess grade I in nine patients, grade II in 11, grade III in five, and grade IV in one. Procedural complications and neurological events during the perioperative and follow-up period were recorded. Combination with bare platinum coils and balloon-assisted technique (BAT) was permitted at the discretion of the attending physician at each center.

Exclusion Criteria

Stent-assisted procedures, retreatment, patients treated with non-Cerecyte bioactive coils, non-saccular aneurysms, and pseudoaneurysms were excluded.

Aneurysm Size

Aneurysms were classified as small (<10 mm) with either a narrow neck (<4 mm) [29 cases] or a wide neck (>4 mm) [19 cases] as previously reported by Murayama et al⁴

Volumetric Study and Packing Density Calculation

Aneurysm sac volume was calculated according to the formula $AV = \frac{4}{3} \times 3.14 \times (\text{length}/2) \times (\text{width}/2) \times (\text{height}/2)$. Volumetric percentage occlusion (VPO) was calculated assuming a cylindrical coil shape (coil radii were obtained from the coil manufacturers). The percentage bioactive coils (PBC) against all coils employed was also calculated in each case.

Procedure

Interventions were performed using angiography units with 3D capability. All procedures were performed via a transfemoral approach under general anesthesia with systemic heparinization (200-250 ACT control). Standard endovascular treatment procedures were used, and aneurysms were occluded with coils packed as densely as possible. Balloon-assisted coiling (HyperForm or HyperGlide, Micro Therapeutics Inc., Irvine, CA, USA) was employed in 29 cases (60.4%) using a single 6 F 0.70 inner lumen guiding catheter (Envoy, Cordis, Miami Lakes, FL, USA). Single antiplatelet therapy (100 mg aspirin/24 h) was administered for six weeks after treatment in cases of wide-neck aneurysms and also in cases in which thromboembolics resolved complications or coil protrusion into the parent vessel occurred.

Angiographic Results

Initial and follow-up angiographic results were evaluated by two external interventional neuroradiologists (A.G. and A.M.) at the Angiographic Core Laboratory. Results were rated according to the Raymond scale:

- Complete occlusion: No contrast filling of the aneurysm.
- Neck remnant: A small amount of contrast filling at the aneurysm neck.
- Incomplete occlusion: Any amount of contrast filling in the aneurysm dome.

Recanalization was defined here as any worsening in the Raymond scale grade, along

with any increase in remnant size despite an unchanged Raymond scale grade, to ensure that no unfavorable change in angiographic stability during follow-up would go undetected. Recanalization was defined as major where any increase in size made retreatment with coils theoretically feasible. Recanalization versus non-recanalization as well as VPO and PBC values were compared using Student's t-test for continuous variables. An a level of $p < 0.05$ was deemed statistically significant.

Follow-up

Clinical and angiographic follow-up was performed in all 48 cases.

Results

Feasibility and Efficacy of Treatment

In our series no early bleeding or rebleeding was reported in any of the 48 cases during follow-up.

In two small aneurysms (3 mm in diameter), a 3 mm spherical Cerecyte coil was unsuccessfully used as the initial coil due to problems related to microcatheter pull-out. In these cases, conventional 3 mm platinum coils were deployed and microcatheter stability improved.

Procedural Complications

Technical complications occurred in five patients (10.4%). Four local thromboembolic complications (8.3%) were resolved with medication without clinical consequences. One case of asymptomatic coil protrusion into the parent vessel was recorded.

One patient suffered a new neurological deficit due to occlusion of the anterior choroidal artery during repair of a ruptured anterior choroidal aneurysm, with severe hemiparesis (a 2.1% clinical complication rate).

Immediate 30-Day Clinical Outcome

There were no deaths related to the procedure. Forty-six patients (97.8%) were neurologically unchanged or improved immediately after the procedure. No cases of meningeal syndrome were reported. One patient underwent severe symptomatic vasospasm that resolved with medical treatment. At discharge the patient with occlusion of the anterior choroidal artery suffered severe hemiparesis and was moderately to severely disabled (mRS 4). No immediate worsening occurred in the five cases

Figure 1 Immediate angiographic outcome. Complete occlusion was achieved in 33 aneurysms (69%), a neck remnant was detectable in 12 (25%), and incomplete occlusion occurred in 3 cases (6%).

that presented with III cranial nerve paresis. Four patients in this group improved and one remained unchanged 30 days after treatment.

Immediate Angiographic Outcome

The immediate angiographic outcome achieved was 33 complete obliterations (68.7%), 12 residual necks (25%), and three incomplete occlusions (6.25%) [Figure 1].

Volumetric Percentage Occlusion

The mean volumetric percentage occlusion (VPO) was 25.2%. In the cases treated using BAT the mean VPO was 27.8% as opposed to 21.8% in the cases treated using conventional coil packing only ($p < 0.01$).

Mid-Term Clinical Outcome

No mild mid-term bleeding or rebleeding was reported. In the patient discharged with moderate to severe hemiparesis, the crural paresis improved, though the brachial paresis remained severe (mRS 4 unchanged). In the five cases with mass effect, III cranial nerve paresis fully resolved in four patients and remained unchanged in one.

Six-Month Angiographic Outcome

Angiographic follow-up studies of the 48 aneurysms were obtained at six months: 33 aneurysms (68.7%) remained completely occluded, 13 (27.1%) had a residual neck, and two (4.16%) were incompletely occluded (Figure 2).

The angiographic stability rate at six months was 66%. Progressive occlusion occurred in eight cases (16.7%).

A further eight cases (16.7%) showed some degree of recanalization. Six aneurysms (12.5%) that initially were completely occluded devel-

Figure 2 Six-month follow-up angiographic results. Six months after the procedure, 33 aneurysms exhibited complete occlusion of the sac (69%), 13 presented a neck remnant (27%), and 2 cases were classified as incomplete occlusion (4%).

Figure 3 Six-month follow-up angiographic results. Six months after the procedure, 32 aneurysms (66%) remained stable with the same Raymond sac occlusion scale grade; 8 (17%) exhibited progressive occlusion, earning a better Raymond scale grade than they had received immediately after the procedure, and 8 (17%) exhibited recanalization. Six of the eight recanalizations (13% of the entire series) were minor recanalizations and 2 (4.2% of the entire series) were major recanalizations. The retreatment rate assumed for this study was therefore 4.2%.

Figure 4 Volumetric percentage occlusion (VPO) and angiographic progression at six months. Angiographically stable aneurysms had an average VPO of 23.9%, cases presenting major or minor recanalization had a VPO of 26.4%, and aneurysms that exhibited progressive occlusion had an average VPO of 27.2%. The differences were statistically non-significant in all cases ($P > 0.05$).

opened residual necks (minor recanalizations) that went untreated. One residual neck and one initially complete obliteration developed into incomplete occlusion (a major recanalization-retreatment rate of 4.2%). Of the three initially incomplete obliterations, two developed into complete occlusion and one into a residual neck (Figure 3).

VPO and Angiographic Stability

The VPO was 23.9% in the cases that were angiographically unchanged, 27.2% in the cases that underwent progressive thrombosis, and 26.4% in the cases in which recanalization occurred. There were no statistically significant differences among the three groups, but there was a statistical trend towards greater percentage occlusion in the cases with progressive thrombosis ($P = ns$) [Figure 4].

Percentage Biologically Active Coils and Angiographic Changes

The percentage biologically active coils (PBC) was 75.1% in the angiographically unchanged aneurysm cases, 74.3% in the recanalization cases, and 93.8% in the progressive thrombosis cases.

In the cases that underwent progressive thrombosis the PBC was higher than in the angiographically stable and recanalization groups ($p < 0.05$).

The difference between the angiographically stable and recanalization groups was not statistically significant (Figure 5).

Figure 5 Percentage Cerecyte coils (PBC). Breakdown of the percentage Cerecyte coils versus bare platinum coils used to embolize each aneurysm according to angiographic progression of the cases at six months. Angiographically stable aneurysms had an average packing with Cerecyte coils, similar to the rate of 74.28% in those with major or minor recanalization. Cases improving their Raymond scale grade displayed significantly higher average percentage packing with Cerecyte coils (93.83%) [$P < 0.05$].

Discussion

Large and giant aneurysms have not been included in this registry. The main reason was the exclusion criteria of the SPAREC study, which was intended to evaluate Cerecyte coils without any additional supporting device that might bias device performance and the results (only BAT was allowed). At participating centers, large and giant aneurysms were usually treated by a variety of endovascular and/or surgical approaches that included stent support combined with endosaccular treatment, parent vessel sacrifice with or without extra-intracranial by-pass and others. However, small aneurysms represent more than 90% of cases in daily neurointerventional practice (93% of aneurysms in ISAT were smaller than 10 mm)¹.

Combined packing with platinum coils at the discretion of the physician in charge was accepted, because the theoretical benefits of "bioactive" devices of this kind have not been demonstrated in the literature, and consequently in our opinion a possible higher rate of initially incomplete occlusions based on an anticipated subsequent biological effect of the device was not warranted by the scientific evidence currently available.

The results are difficult to compare with the literature results for bare platinum coils for a variety of reasons (single-center retrospective studies by skilled neurointerventionists; types of patients and aneurysms treated; complication assessment methodology used; differing definitions of the terms employed, especially for angiographic follow-up, and differing definitions of recanalization). Despite the intrinsic limitations of a non-randomized observational registry, our multicenter study design included external analysis of the angiographic results in order to minimize operator-related bias. The results have been compared to different series reported in the literature.

Series Comparisons

ISAT Data^{1,2,3}

Guglielmi detachable coils (GDCs) [Boston Scientific/Target, Fremont, CA, USA] were introduced for clinical use in 1992 and are the "gold standard" for endovascular repair of cerebral aneurysms⁵. ISAT was the most important study comparing endovascular occlusion using bare platinum coils to surgical clipping pub-

lished in the medical literature. ISAT showed that, compared with surgical clipping, endovascular coil embolization of ruptured intracranial aneurysms lowered the risk of death and/or disability by 7.4% in the first year in a total of 2143 patients (1073 endovascular aneurysm repairs and 1070 surgical aneurysm repairs).

Angiographic follow-up in the ISAT study over four years yielded 66% complete obliterations, 26% residual necks-subtotal obliterations, and 8% incomplete occlusions in the endovascular group opposed to 82% complete obliterations, 12% residual necks, and 6% incomplete occlusions in the surgical group. The rebleeding rate in the endovascular patients was 0.2% patient/year, a rate that did not differ significantly from the surgical group (three of 1012 patients treated surgically compared with seven of 1096 patients treated endovascularly).

The retreatment rate in the ISAT study was 17.4% in the endovascular group (8.8% early and 9% late retreatment) compared with 3.8% in the surgical group. The initial outcome was associated with the frequency of retreatment: 5.8% of complete obliterations, 20.6% of residual necks, and 18.8% of incomplete occlusions required retreatment. Procedural complications occurred in 6% of the retreatments and resulted in transient neurological symptoms only. Less than 50% of recurrences were of sufficient concern to warrant retreatment. Predictors of retreatment were younger age, large aneurysm size, incomplete initial occlusion, and posterior communicating aneurysms. Wide-neck aneurysms did not require more frequent retreatment.

Bare Platinum Coil Series

The largest single-center series (818 patients with 916 aneurysms) assessing the durability of aneurysm embolization with bare platinum coils was reported by Murayama et al⁴. They reported a 5.1% recanalization rate for small aneurysms with narrow necks, a 20% recanalization rate for small, wide-neck aneurysms. The technical complication rate was 8.4%, cerebral thromboembolic embolization being the most common complication. In their experience most recanalizations occurred within three months. The incidence of delayed rupture was 1.6%, with ten out of 12 delayed ruptures being large or giant aneurysms.

These same authors reported the natural history (mean duration of angiographic follow-up:

17.3 months) of 73 aneurysms with neck remnants after embolization⁶. The recanalization rate was 17% for small aneurysms with narrow necks and 43% for small aneurysms with wide necks.

Byrne et al⁷ presented a series of 259 aneurysms with six months angiographic follow-up. They reported a recurrence rate of 13.6% for small aneurysms and 14.8% for large aneurysms, with 8.5% improved occlusion during follow-up. Annual rebleeding rates were 0.8% in the first year, 0.6% in the second year, and 2.4% in the third year. A total of 0.4% of 221 stable occluded aneurysms reruptured. The incidence of rebleeding was 7.9% in patients with unstable aneurysms (defined as an increase in the amount of contrast filling the aneurysm relative to the preceding angiogram). The retreatment rate was 5%.

Raymond et al⁸ reported a 21.3% recanalization rate for small aneurysms (10.9% major recurrences) and a 23.7% recanalization rate for lesions with a neck size <4 mm (13.3% major recurrences). The “best” aneurysmal characteristics, such as small sac size and small neck size, were associated with a recurrence rate >20% in a series of 383 patients with angiographic follow-up (277 cases followed for more than one year). In this series only 46.9% of recurrences were evident at six months, and the authors pointed out that six months’ angiographic follow-up was clearly insufficient. The most significant predictors of recurrence were intervention during the acute phase, aneurysm size, suboptimal initial angiographic outcome, and length of the follow-up period. Age, sex, and location had no significant influence on recurrence. The rebleeding rate was 0.8% over a mean observation period of 31.3 months.

PGA-Platinum Coil Series

“Bioactive” embolization coils represent a change from inert bare platinum coils. These coils have been designed with the theoretical purpose of speeding up the process of intra-aneurysmal healing. The first of these devices was the Matrix Detachable Coil (MDC) [Boston Scientific/Target, Fremont, CA, USA]. The first generation of this device consisted of a bare platinum core coated with a bioabsorbable polyglycolic/polylactic acid (PGLA) polymer that made up 70% of the total coil volume. In animal models this material resulted in accelerated intra-aneurysmal healing⁹.

Fiorella et al¹⁰ reported a 36.6% recanalization rate and a 23.1% retreatment rate using MDC in 82 cases with angiographic follow-up. The recanalization rate for small, narrow-neck aneurysms was 26.1%, with a 13.8% retreatment rate. They hypothesized that these results may have been attributable to undercoiling, but they did not find differences in packing density in patients with recurrences and those without. The recanalization and retreatment rates were unexpected, and the authors also postulated possible “matrix responder and non-responder” groups, bearing in mind that PGA accounted for 70% of coil volume and that packing density declined as the bioactive component was absorbed and volume decreased.

Murayama et al¹¹ reported results for the MDC in 118 aneurysms (87 with angiographic follow-up), 73.9% being small aneurysms. The recanalization rate eight months after the initial procedure was 19.5%. The recanalization rate for aneurysms originally diagnosed as having a neck remnant was 15%, while the recanalization rate for residual aneurysm was 38%. No recanalization was observed in aneurysms that had been completely occluded with Matrix coils. The technical complication rate was 5% with an overall morbidity of 3.6%.

Mitra et al¹² reported their results for a total of 84 aneurysms (91.6% small aneurysms) treated with MDC (46 with MDCs only and 38 in combination with other devices). For a total of 70 angiographic follow-up studies the recanalization rate was 24.3% (17 recanalized aneurysms, 80% being small) and an 8.6% recanalization rate for large aneurysms. The recanalization rate for the aneurysms that initially were completely obliterated was 22% (2.4% major recanalizations). The recanalization rate for aneurysms with residual necks during follow-up was 25% (6.2% major recanalizations). Where initial occlusion was incomplete, the recanalization rate was 30.8% (all major recanalizations).

Niimi et al¹³ reported the results obtained using the Matrix coil in 47 angiographically followed aneurysms (mean: 12.2 months; range: 0-34 months). The overall recanalization rate was 33% for small, narrow-neck aneurysms and 63% for small, wide-neck aneurysms, with a periprocedural morbimortality of 2.8%.

Bendszus et al¹⁴ reported results for 55 aneurysms (mean size 5.5 mm) repaired with Cerecyte coils and compared these results with

a previous series repaired with bare platinum coils at the same institution. The six-month retreatment rate with Cerecyte coils dropped to 2% ($p=0.056$) compared with 11% in the cases in which conventional platinum coils were used alone. The complete occlusion rate for the six-month period was 78% opposed to 62% in the cases repaired with conventional platinum coils only ($p=0.0045$). No differences in the periprocedural complication rate were observed between the two groups.

Butteris et al¹⁵ reported results of 68 aneurysms treated with a mixture of Cerecyte and bare platinum coils. Follow up angiography was available in 46 cases at six months and 70.6% had stable occlusion, 8.8% had improved occlusion and 20.6% had worsening occlusion. No cases of rebleeding were reported.

Veznedaroglu et al¹⁶, reported results obtained using Cerecyte coils in 89 aneurysms with 7 mm mean size (65% ruptured lesions). Mean angiographic follow-up was 11.2 months and retreatment rate was 6.7%.

SPAREC Data

Safety and Performance of Cerecyte Coils

There was no increased friction during Cerecyte coil manipulation, and handling was similar to that of conventional platinum coils at all stages of the procedure. This is probably related to PGA location within the loops of the platinum winding. However, in two small aneurysms the initial basket could not be formed using 3 mm spherical Cerecyte coils, and finally a 3 mm spherical bare platinum coil was deployed initially with better results. This may reflect a slight initial stiffness to Cerecyte coils that is not noticeable when they are deployed in larger aneurysms.

The data from this study revealed a technical complication rate and immediate and mid-term clinical outcomes similar to those for patients treated with bare platinum coils⁴. The technical complication rate was 10.4% (five cases) and the most frequent was thromboembolism, which occurred in four cases: one case of aneurysm remodeling and three cases of non-remodeling (an 8.2% thromboembolism complication rate). One asymptomatic coil protrusion also occurred. The clinical complication rate related to the procedure was 2.1%.

In our experience the use of BAT does not increase the rate of thromboembolic events.

Albayran et al¹⁷ reported that the risk of thromboembolic events during BAT treatment of intracranial aneurysms was not higher than for conventional techniques alone, and the only variables found to influence this risk were microcatheter repositioning, coil removal, and repositioning and aneurysm neck size. Layton et al¹⁸ also reported no statistically significant difference in rates of thrombus formation in patients treated using BAT. Sluzewski et al¹⁹ reported a 14.1% thromboembolic complication rate during balloon-assisted coil embolization (mean size of lesions treated 11.7 mm).

Clinical Efficacy-Rebleeding

No cases of early bleeding or midterm rebleeding were reported in our study.

Preventing bleeding is the principal clinical goal of intracranial aneurysm repair. The safety of standard platinum coils in preventing bleeding is unquestioned. Despite worse angiographic results than with surgery, with more recurrences and incomplete occlusions, the clinical consequences were negligible. Long-term risk of rebleeding in coil-occluded aneurysms was more frequent with endovascular coiling (0.2% per patient/year) according to the ISAT data², but not statistically different from the surgically treated group.

The Cerebral Aneurysm Rerupture After Treatment (CARAT) study²⁰ reported a 0.11% annual hemorrhage rate for aneurysms repaired endovascularly. Combining the one-year ISAT rebleeding rates with those in the CARAT study and assuming that 60% of rebleedings will yield new morbimortality, the reduced morbidity achieved by endovascular repair in the first year compared with conventional surgery (a 7.4% reduction in absolute risk) is equivalent to a duration of the initial benefit for 73 years.

Mid-Term Follow-up of Aneurysms

Treated with Cerecyte Coils - Recurrences

Recanalization after coil occlusion is a major drawback of endovascular treatment and ranges between 17 and 33%^{2,8}. According to ISAT data retreatment rate is at least five times higher in cases treated by endovascular techniques compared to conventional surgical clipping³.

The SPAREC study recorded only small aneurysms that are less likely to recanalize.

Eight cases (16.7%) exhibited some degree of recanalization at six months: two cases developed major recanalization (a 4.2% retreatment rate) and six cases (12.5%) developed minor recanalization (according to the Raymond scale, residual necks that are left untreated). Overall, at six months 33 aneurysms (68.7%) were completely occluded, 13 (27.1%) had a neck remnant, and two (4.2%) were incompletely occluded.

Angiographic results were similar to the ISAT results² for an average follow-up of four years except for the incomplete occlusion rate (8% vs. 4.2%). Nevertheless, these angiographic results are not comparable, because on angiography 26% of the ISAT cases exhibited a residual neck with minor residual sac filling. According to the SPAREC study angiographic criteria, following the Raymond scale, any amount of sac filling on follow-up angiograms was classified as incomplete occlusion.

Our data compare favorably with most platinum coil series. Raymond et al's GDC series⁸ furnished the historical bare platinum coil study most comparable to the SPAREC data, because both studies used the same method to assess recanalization. In this series the "best" aneurysmal characteristics, e.g., small size and a narrow neck, were associated with a recurrence rate above 20% (11% major recurrences), but only 46.9% of recanalizations were evident at six months.

SPAREC recurrence data compare favorably with Fiorella et al and Niimi et al MDC series^{10,13} and are similar to Murayama et al Matrix series¹¹ but are worse than the findings reported by Bendszus et al. for Cerecyte coils¹⁴.

Factors Influencing Recanalization

No statistically significant differences were observed in the recanalization rate with neck size or the neck-to-sac ratio. At the present time the use of balloon-assisted techniques by experienced neuroradiologists makes feasible coil embolization of the vast majority of small saccular aneurysms.

The mean VPO in the SPAREC study was 25.2%. The VPO was 23.9% in the angiographically stable cases, 27.2% in the cases that underwent progressive thrombosis, and 26.4% in the cases that underwent recanalization. No statistically significant differences ($P=ns$) were observed among these three subgroups, though there was a statistical trend towards higher

VPO values in the cases with progressive thrombosis.

Several authors have pointed out the influence of VPO on angiographically stable follow-up. Sluzewski et al²¹ reported no compaction for small aneurysms with volumes smaller than 200 mm³ and 20% packing at six month's angiographic follow-up. For aneurysms with volumes smaller than 600 mm³, no compaction occurred where packing attained 24% of volume. Yutaka et al²² studied the correlation between the coil packing ratio and coil compaction in 62 patients with ruptured, small, narrow-neck aneurysms after GDC embolization. Compaction was visible angiographically in 25.8% of patients. In cases with higher compaction (9%), defined as more than 2 mm reappeared space in the embolized aneurysm, the mean packing ratio was less than 50%.

The cases in which BAT was employed had a mean VPO of 27.8% compared with 21.8% for cases treated conventionally ($P<0.05$). Sluzewski et al²¹ reported no differences between mean packing density in remodeled aneurysms (22.7%) vs. aneurysms repaired using conventional techniques (24.1%). However, the two series are not comparable, especially with respect to mean size of the aneurysms included, which was 11.7 mm in their series¹⁴.

The 33 SPAREC cases with initially complete obliteration had an angiographic stability rate of 78% (26 cases), with 18% minor recanalizations (six residual necks) and 3% major recanalizations (one case). Six of the 12 cases with an initial residual neck remained stable, five progressed to complete occlusion (a 91% angiographic stability and improvement rate), and one developed major recanalization (an 8% major recanalization rate for initial residual necks). Two of the three cases with initially incomplete occlusion progressed to complete obliteration, while a residual neck developed in the other. The initial angiographic outcome had no influence on the major recanalization rate ($P=ns$).

The PBC in the cases with progressive thrombosis was higher than the percentage used in the stable group and the recanalization group ($P<0.05$), while it did not differ statistically for the angiographically stable and the recanalization groups. Cerecyte coils, contain the same volume of platinum as conventional coils. The added presence of PGA may help to promote intra-aneurysmal healing in patients who

are "PGA responders". Following absorption of the bioactive component, the expected results should be at least the same as those obtained using bare platinum in "non-PGA responders" (Figure 5).

Retreatment Rate

The retreatment rate in the SPAREC study was 4.2% at six months.

In ISAT³ the retreatment rate for the endovascular coiling group was 17.4% (8.8% early and 9% late retreatments). The statistically significant factors for predicting future retreatment in the endovascular treatment group were aneurysm size, initial angiographic outcome, initially incomplete occlusion, patient age, and origin on the posterior communicating artery.

The CARATS investigators²⁰ reported an annual retreatment rate for coiling of 13.3% during the first year, 4.5% during the second year, and 1.1% thereafter.

We intend to extend angiographic follow-up to one year in cases in which angiographic results are stable and to 18 months in cases in which angiographic results indicate instability at one year. Assuming future angiographic findings similar to those in Raymond et Al series⁸, i.e., only half of the recanalizations being detectable at six months, the one-year retreatment rate can be expected to rise to around 8-9% (6.7% in Veznedaroglu¹⁶ Cerecyte series with 11.2 months angiographic follow up period). If this turns out to be the case, it would mean a 50% reduction in the ISAT retreatment rate³ and a 30% reduction in the CARATS retreatment rate²⁰.

What percentage reduction in the recanalization rate would make the cost:benefit ratio of using the new bioactive coils worthwhile? Use would probably become cost effective at a five to 10% reduction in the recanalization rate, but a sample size of over a thousand patients would be required to attain sufficient statistical power, and such endovascular therapy trials as HELPS, the Cerecyte trial, and the MAPS trial are each planning to enroll 500-630 patients.

There is thus some uncertainty as to which recanalizations require treatment that will not be cleared up based on the scientific data that will be forthcoming in the next few years, because the clinical significance of recanalization has not yet been definitely determined. Whe-

ther retreatment is appropriate will therefore continue to be subject to a number of factors which are difficult to quantify and may be interpreted differently even by experienced neuroradiologists. In ordinary daily practice, stable residual necks and minor recanalizations are left untreated, with most retreatments involving major recanalizations and incomplete occlusions. In future trials systematic assessment of the results achieved for intracranial aneurysms using endovascular coil therapy should include the retreatment rate, along with rebleeding and recanalization, as an adverse event in patient progress.

In spite of the limitations inherent in a non-randomized study with a small number of cases, in our opinion these preliminary data suggest a low recanalization rate with no increase in the procedural complication rate, and hence a larger randomized controlled trial is warranted.

Conclusions

New embolic agents should first demonstrate safety levels equivalent to those of standard platinum coils before they are considered for widespread use. The primary objective of endovascular therapy should be to extend and improve long-term efficacy without any compromise of safety. The SPAREC study results show that:

- The technical complications and immediate clinical outcomes for Cerecyte coils were similar to those for bare platinum coils;
- No bleeding or rebleeding was recorded during six months' follow-up;
- The overall recanalization rate at six months was 16.7% (12.5% minor recanalizations and 4.2% major recanalizations);
- The six-month retreatment rate was 4.2% for small aneurysms (wide and narrow necks);
- The PBC was higher in cases with progressive thrombosis ($P < 0.05$);
- BAT increased the VPO ($P < 0.05$) without increasing the thromboembolic complication rate.

Acknowledgement

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References

- 1 Molyneux 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* 26; 360(9342): 1267-1274, 2002.
- 2 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(9499): 809-817, 2005.
- 3 Campi A, Ramzi N et Al: Retreatment of Ruptured Cerebral Aneurysms in Patients Randomized by Coiling or Clipping in the International Subarachnoid Aneurysm Trial (ISAT). *Stroke* 38(5): 1538-1544, 2007.
- 4 Murayama Y, Nien YL et Al: Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. *J Neurosurg* 98(5): 959-966, 2003.
- 5 Guglielmi G, Viñuela F, Dion J: Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: preliminary clinical experience. *J Neurosurg* 75: 8-14, 1991.
- 6 Hayakawa M, Murayama Y et Al: Natural history of the neck remnant of a cerebral aneurysm treated with the Guglielmi detachable coil system. *J Neurosurg* 93(4): 561-568, 2000.
- 7 Byrne J, Sohn M, Molyneux A: Five year experience in using coil embolization for ruptured intracranial aneurysms: outcomes and incidence of late rebleeding. *J Neurosurg* 90: 656-663, 1999.
- 8 Raymond J, Guilbert F et Al: Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. *Stroke* 34: 421-427, 2003.
- 9 Murayama Y, Tateshima S et Al: Matrix and bioabsorbable polymeric coils accelerate healing of intracranial aneurysms: long-term experimental study. *Stroke* 34(8): 2031-2037, 2003.
- 10 Fiorella D, Albuquerque F, McDougall C: Durability of aneurysm embolization with Matrix detachable coils. *J Neurosurg* 58: 51-59, 2006.
- 11 Murayama Y, Viñuela F et Al: Initial clinical experience with Matrix coils for the treatment of intracranial aneurysms. *J Neurosurg* 105(2): 192-199, 2006.
- 12 Mitra D, Herwadkar A et Al: Follow-up of intracranial aneurysms treated with Matrix detachable coils: A single center experience. *Am J Neuroradiol* 28(2): 362-367, 2007.
- 13 Niimi Y, Song J et Al: Endosaccular treatment of intracranial aneurysms using Matrix coils: Early experience and midterm follow-up. *Stroke* 37: 1028-1032, 2006.
- 14 Bendszus M, Bartsch A, Solymosi L: Endovascular occlusion of aneurysms using a new bioactive coil. *Stroke* 38: 2855-2857, 2007.
- 15 Butteris 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: 53-56, 2008.
- 16 Veznedaroglu E, Koebbe C et Al: Initial experience with bioactive Cerecyte detachable coils: impact on reduction recurrence rates. *Neurosurgery* 62: 799-806, 2008.
- 17 Albayram S, Selcuk H et Al: Thromboembolic events associated with balloon-assisted coil embolization: evaluation with diffusion-weighted MR imaging. *Am J Neuroradiol* 25(10): 1768-1777, 2004.
- 18 Layton KF, Cloft HJ et Al: Balloon-assisted coiling of intracranial aneurysms: evaluation of local thrombus formation and symptomatic thromboembolic complications. *Am J Neuroradiol* 28(6): 1172-1175, 2007.
- 19 Sluzewski M, van Rooij WJ et Al: Balloon assisted coil embolization of intracranial aneurysms: incidence, complications and angiography results. *J Neurosurg* 105: 396-399, 2006.
- 20 The CARAT Investigators: Rates of delayed rebleeding from intracranial aneurysms are low after surgical and endovascular treatment. *Stroke* 37: 1437-1442, 2006.
- 21 Sluzewski M, van Rooij WJ et Al: Relation between aneurysm volume, packing and compaction in 145 cerebral aneurysms treated with coils. *Radiology* 231: 653-658, 2004.
- 22 Yutaka K, Hamada JI et Al: Evaluation of the stability of small ruptured aneurysms with a small neck after embolization with Guglielmi detachable coils: Correlation between coil packing ratio and coil compaction. *J Neurosurg* 56(4): 785-792, 2005.

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