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Brain Aneurysms and Arteriovenous Malformations

Advancements and Emerging Treatments in Endovascular Embolization

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Background and Purpose—Brain aneurysms and vascular malformations can cause cerebral hemorrhages, with devastating consequences for the patients and their families. Since the development of microcatheters and materials used for endovascular embolization, we have witnessed a rapid advancement in the technology and in the number or patients treated with this approach. The aim of this review is to survey recent data relevant to new technologies and emerging treatment strategies in these areas.

Summary of Review—Clinical trials assessing the safety and efficacy of coil embolization for cerebral aneurysms were based on the use of bare platinum, helical coils. Since then, endovascular operators have been testing and using new materials such as bioactive coils, expandable coils, and complex-shaped coils. Based on the data so far obtained, third and fourth generation coil designs are rapidly emerging and will be ready for clinical application in the near future. Balloon- and stent-assisted coil embolization is enabling the treatment of complex, large-neck aneurysms and the vascular reconstruction of lesions previously considered not treatable. New open- and closed-cell designs allow the navigation and deployment of stents in extremely tortuous vessels. With regards to the embolization of vascular malformations, it is possible to safely navigate microcatheters and microwires through very small arteries previously considered not accessible. In addition, embolization materials such as n-butyl cyanoacrylate and ethylene-vinyl alcohol copolymer are now routinely injected to safely reduce or obliterate large and complex arteriovenous malformations and fistulae.

Conclusions—Advancements in technology are rapidly improving the endovascular approach to the treatment of cerebral aneurysms and arteriovenous malformations. **(*Stroke*. 2007;38:1411-1417.)**

Key Words: aneurysm ■ AVM ■ coil ■ NBCA ■ ONYX ■ matrix ■ subarachnoid hemorrhage ■ cerebral hemorrhage

According to angiographic and autopsy studies, intracranial aneurysms have a prevalence of between 0.5% and 6%. Most unruptured aneurysms remain undetected; however, increasing numbers of aneurysms are detected incidentally during neuroimaging studies. A minority of aneurysms are detected when they cause symptoms either by cranial nerve compression or when they rupture, causing a subarachnoid hemorrhage (SAH). Aneurysmal SAH (aSAH) can have devastating consequences, with a reported case fatality of 32% to 67% and a 10% to 20% long-term dependence in survivors.[1–4]

The first description of the endovascular approach to embolize cerebral aneurysms was made by Fedor Serbinenko in 1971.[5] The Russian neurosurgeon described the use of detachable balloons to occlude either the aneurysmal sac or the parent vessel. In 1991 Guido Guglielmi introduced the use of detachable coils for the treatment of intracranial aneurysms.[6–7] As described by the authors, platinum coils were inserted into the aneurysmal sac and separated from a stainless steel introducer by electrochemical detachment. Initially, the treatment was reserved for aneurysms judged to be at too high a risk for microsurgical clipping. However, as technology and the operator's ability improved, the use of detachable coils rapidly spread. Ten years after its first description, it was estimated that 1500 patients per month were treated with endovascular embolization worldwide.[8]

To compare the safety and efficacy of endovascular embolization versus microsurgical clipping, the International Subarachnoid Aneurysm Trial (ISAT) investigators undertook the first multicenter, randomized trial,[9] which involved 42 centers in Europe and North America. The trial enrolled 2143 patients and randomly assigned them to neurosurgical

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clipping (n=1070) or endovascular embolization with bare platinum coils (n=1073). The clinical outcomes were assessed at 2 months and at 1 year, with interim ascertainment of rebleeding and death. The primary outcome was a modified Rankin Scale score of 3 to 6 (dependency or death) at 1 year. Trial recruitment was stopped early by the steering committee after a planned interim analysis revealed worst outcomes in the neurosurgical group. In particular, 190 of 801 (23.7%) patients in the endovascular arm were dependent or dead at 1 year compared with 243 of 793 (30.6%) treated with microsurgical clipping ($P=0.0019$).[9] The relative and absolute risk reductions in dependency or death after allocation to an endovascular versus surgical treatment were 22.6% (95% CI, 8.9 to 34.2) and 6.9% (2.5 to 11.3), respectively.[9]

The data from ISAT were the subject of debate in the literature.[10–11] Those in disagreement with the trial's results mainly argued that (1) the outcome of the surgical arm of ISAT was worse than the previously published data, (2) the location of the aneurysms randomized to both treatments was biased for not being representative of the general population of patients with aSAH, (3) the long-term outcome of the endovascular treatment was unknown, and (4) the majority of patients screened were not subject to randomization.

Although enrollment in ISAT was halted, the investigators continued their long-term follow-up analysis on the patients enrolled. The data published in 2005 showed that the early survival advantage of the endovascular group was maintained for up to 7 years and remained significant (log rank, $P=0.03$).[12] The absolute reduction in the risk of death or dependency increased to 7.4% in the endovascular arm. The risk of epilepsy was substantially lower in patients treated with coil embolization. However, the risk of rebleeding at follow-up (7 years) was slightly higher in the endovascular arm, 0.2% per patient-year as compared with surgical clipping, 0.1% per patient-year (log rank, $P=0.22$).[12]

The Cerebral Aneurysmal Rupture After Treatment (CARAT) investigators compared rerupture rates after aSAH.[13] In an ambidirectional cohort study, 9 institutions identified all ruptured saccular aneurysms treated between 1996 and 1998. A total of 1010 patients (711 surgically clipped, 299 treated with coil embolization) were contacted by written questionnaire or telephone. A neurologist, neurosurgeon, and neurointerventional radiologist independently adjudicated possible reruptures. Rerupture of the treated aneurysm after 1 year occurred in 1 patient treated with coil embolization during 904 person-years of follow-up (annual rate, 0.11%) and in no patients treated with surgical clipping during 2666 person-years ($P=0.11$). Aneurysm retreatment after 1 year was more frequent in patients treated with coil embolization; however, major complications were rare during retreatment. The authors concluded that late events are unlikely to overwhelm differences between the procedures at 1-year follow-up.[13]

Van Der Shaf et al recently reviewed randomized trials comparing coiling versus microsurgical clipping in patients with aSAH using the Cochrane Stroke Group Trials Register, MEDLINE, and EMBASE.[14] The analysis included 2272 patients (range per trial: 20 to 2143). At 1-year follow-up evaluation, the relative risk of poor outcome for coiling versus clipping was 0.76 (95% CI, 0.67 to 0.88). The absolute risk reduction was 7% (95% CI, 4% to 11%). For patients with SAH secondary to ruptured, anterior circulation aneurysms, the relative risk of poor outcome was 0.78 (95% CI, 0.68 to 0.90) and the absolute risk decrease was 7% (95% CI, 3% to 10%). For posterior circulation aneurysms, the relative risk was 0.41 (95% CI, 0.19 to 0.92) and the absolute decrease in risk was 27% (95% CI, 6% to 48%).

Unruptured Intracranial Aneurysms

To treat or not to treat unruptured intracranial aneurysms (UIA) is still a matter of debate.[15–17] In 2000 the Stroke Council of the American Heart Association published guidelines for the treatment of UIA.[16] Currently, Raymond et al are investigating these issues in a randomized trial.[18] The discussion of the variables that play a role in the decision on whether to treat UIA is beyond the scope of this review. With regards to the safety and efficacy of the endovascular treatment for UIA, several authors indicate an overall 5% to 10% risk of morbidity, mostly secondary to embolic phenomena, and near 0% mortality.[19–23] In the largest data set so far, Johnston et al evaluated the safety of the endovascular treatment compared with microsurgical clipping in 2069 patients treated in California hospitals for UIA from 1990 to 1998.[24] In-hospital mortality and discharge to another healthcare facility rather than home were less frequent in the endovascular group (10% versus 25%; $P<0.001$). Mortality was 0.5% in the endovascular group compared with 3.5% of patients that underwent traditional clipping ($P<0.001$).[24] In a meta-analysis of 48 studies over a 7-year period, Brilstra et al reported a 6.7% rate of permanent complications for endovascular treatment.[19] The International Study of Unruptured Intracranial Aneurysms (ISUIA) reported a 9.5% overall rate of morbidity and mortality at 1 year after the endovascular treatment of UIA.[17] Aneurysmal rupture during coil embolization is one of the most feared complications of the procedure. However, previously ruptured aneurysms are at a much greater risk of intraprocedural rupture compared with unruptured aneurysms. In particular, Tummala et al reported a total of 10 intraprocedural ruptures in a series of 734 aneurysms.[25] All ruptures occurred in previously ruptured aneurysms.

Advancements in Technology

Recanalization of the aneurysmal sac is the main drawback of endovascular embolization for both ruptured and UIA, occurring in 4.7% to 38% of cases.[26–28] The exact mechanism of intra-aneurysmal thrombus formation and neo-intimal growth across the neck after coil embolization is not completely understood. It has been hypothesized that decreased blood flow into the aneurysmal sac may initiate thrombosis, subsequent clot organization, and fibrosis.[27–30] However, when these processes do not take place, the force of pulsatile blood flow against inert platinum may cause the coil mass to compact or rearrange. Residual arterial blood flow in the aneurysmal sac is thought to prevent thrombus organization, leading to eventual aneurysmal recanalization and need for retreatment.[27–30]

Achieving a safe and permanent closure of the aneurysmal sac has been the main focus of the research and development of new materials for embolization.

The first described detachable coils (Guglielmi detachable coils; Boston Scientific) were helical-shaped and made of bare platinum. Platinum produces a delayed clot organization and moderate inflammatory response.[27,29] Several strategies have been used to improve aneurysmal sac fibrosis and thus avoid recanalization, such as: (1) increased packing density; (2) the use of coils coated with a bioabsorbable polymeric or expandable material such as hydrogel; (3) cytokines such as growth factors and protein coatings; and (4) fibroblast tissue allografts.[31–39] In particular, bioabsorbable polymer was able to stimulate an inflammatory reaction necessary to promote early fibrosis of the aneurysmal sac in an animal model. Matrix (90% polyglycolide- and 10% polylactide-coated platinum coils; Boston Scientific) was the first coil commercially developed for this purpose.[31] Several single-center series published so far on the use of matrix coils in both ruptured and unruptured aneurysms suggested that the coil has a good safety profile.[39–41] With regards to efficacy, some authors reported recanalization rates higher with matrix compared with bare platinum coils.[40,41] The high recanalization rates were attributed to coil friction and compartmentalization attributable to the high amount of bioabsorbable polymeric coating on the coil. In the new generation of matrix coils, changes in the coil design were made to address these issues. HydroCoil (Microvention/Terumo) is a platinum coil coated with a material (hydrogel) that expands on contact with blood.[32,33] The HydroCoil for Endovascular Aneurysm Occlusion (HEAL) study had enrolled 184 patients with 191 cerebral aneurysms as of February 2004.[33] The preliminary data showed that the initial occlusion and complication rates were not significantly different from aneurysms treated with bare platinum coils. Follow-up angiography is currently being collected to determine whether HydroCoil can reduce the rate of aneurysmal recanalization in their patient population. Recently, Gaba et al reviewed the outcomes of 50 aneurysms embolized primarily using HydroCoil and compared them with aneurysms embolized with bare platinum coils.[32] Embolization with HydroCoil yielded a significantly greater volumetric percentage sac occlusion (84.8% versus 29.8%; $P<0.001$). There were no differences in the length of hospital stay. Follow-up angiography showed that recurrence rates were significantly decreased in small aneurysms in the HydroCoil cohort (5% versus 17%; $P=0.013$).[32] The data have recently spurred debate.[42]

In an in vitro model, a higher packing density and better aneurysmal filling and neck coverage were obtained with the use of complex-shaped platinum coils (Orbit DCS; Cordis Neurovascular, Inc) compared with helical coils.[43] Recently, a single-center prospective study reported on the use of these types of coils to treat 77 aneurysms; follow-up was available in 31 patients.[44] The packing density was $37\pm13.1\%$. No rerupture was observed during the follow-up interval. Recanalization was observed in 4/31 aneurysms (12.9%). Excluding basilar tip aneurysms from the analysis reduced the percentage of recanalization to $<7\%$.

Balloon- and Stent-Assisted Embolization

The endovascular approach for the treatment of complex and large-neck aneurysms is generally considered a challenge. Nondetachable balloons and stents have been used by endovascular operators as an aid to successfully perform coil embolization.[45,46] Moret et al described the technique of temporarily inflating a balloon during coil positioning in order to prevent coil herniation into the parent artery.[45] Balloon-assisted coil embolization can also help to achieve a more stable and higher packing density in these lesions.[45,46] In their series, the authors reported 0.5% morbidity and 0% mortality from the procedure. Angiographic follow-up showed that complete occlusion occurred in 77% of aneurysms, with 17% subtotal occlusion.[45] Cottier et al reported their experience in treating 49 aneurysms with balloon-assisted coil embolization.[46] In their series, 90% of aneurysms that were completely occluded at initial treatment were stable at follow-up evaluation; 15% that were subtotally occluded were recanalized.

Stent-assisted coil embolization was also described as a mean to safely embolize wide-neck or complex aneurysms.[47–49] Stent technology has markedly improved in the last decade. A self-expanding, "open-cell" stent design allows navigation and deployment in tortuous vessels.[48,49] Self-expanding, "closed-cell" stent designs are currently being tested and will be available in the near future.[50] At present, reports from retrospective single-center case series suggest that the stent-assisted coil embolization of large-neck and complex aneurysms is feasible.[47–49] With regards to delayed in-stent stenosis, Fiorella et al reported data from a single-center database of 156 patients in whom a stent was used for treatment of large-neck aneurysms.[49] In their series, 9 (5.8%) developed moderate or severe delayed (>2 months) in-stent stenosis.[49] Two of 9 were symptomatic and were treated with angioplasty. Interestingly, the asymptomatic patients showed partial or complete spontaneous resolution of the stenosis at follow-up imaging.

Endovascular Treatment of Arteriovenous Malformations

It has been reported that 2% of intracranial hemorrhages are caused by a ruptured arteriovenous malformation (AVM).[50–52] Data from the New York Islands AVM Hemorrhage Study suggest that the AVM detection rate is 1.21/100 000 person-years, and the incidence of AVM-hemorrhage is 0.42/100 000 person-years.[53] Data from the prospective, longitudinal, population-based Northern Manhattan Stroke Study suggest that the crude incidence for first-ever AVM-related hemorrhage is 0.55/100 000 person-years. In addition to hemorrhage, 15% to 35% of patients may present with seizures as their first manifestation of a cerebral AVM or ischemia secondary to "steal" phenomenon.[54]

With regards to outcomes from AVM-induced hemorrhages, Choi et al recently reported data on 241 consecutive AVM patients from the prospective Columbia AVM Databank.[55] Among 241 AVM patients, 29 (12%) had subsequent intracranial hemorrhage during follow-up. The authors then compared 84 non-AVM patients with intracerebral hemorrhage from the Northern Manhattan Study (NOMAS) as

control. Among AVM-hemorrhage subtypes, parenchymatous AVM hemorrhage was associated with higher morbidity (odds ratio, 2.9; 95% CI, 1.5 to 5.8 for National Institutes of Health Stroke Scale ≥2) than nonparenchymatous hemorrhages. However, parenchymatous AVM hemorrhages fared better in the long-term than non-AVM hemorrhages.[55]

The natural history of unruptured AVM is unclear. A Randomized Trial of Unruptured Brain Arteriovenous malformations (ARUBA) is underway to address this issue.[56]

Several predictive factors have been reported to be associated with hemorrhage as presentation of an AVM.[57–61] Recently, Stapf et al described their relevance for the risk of subsequent hemorrhages in 622 consecutive patients from the prospective Columbia AVM database.[61] Increasing age (hazard ratio, 1.05; 95% CI, 1.03 to 1.08), initial hemorrhagic AVM presentation (hazard ratio, 5.38; 95% CI, 2.64 to 10.96), deep brain location (hazard ratio, 3.25; 95% CI, 1.30 to 8.16), and exclusive deep venous drainage (hazard ratio, 3.25; 95% CI, 1.01 to 5.67) were independent predictors of subsequent hemorrhage. Annual hemorrhage rates on follow-up ranged from 0.9% for patients without hemorrhagic AVM presentation, deep AVM location, or deep venous drainage to as high as 34.4% for those harboring all 3 risk factors.

Treatment

Treatment modalities for AVMs are surgery, radiotherapy, and endovascular embolization. Such treatments can also be combined and tailored to the particular features of the AVM.[62–67]

Endovascular Embolization

Endovascular embolization is most commonly used to reduce the size of the lesion in preparation for surgery or radiation treatment.[62–67] The first step entails placement of a microcatheter via AVM feeding arteries close to the "nidus", represented by a conglomeration of abnormal arteriovenous connections at the precapillary level. At this point, an embolic agent is infused in the nidus.[62–67] Advancements in the development of microcatheter technology and liquid embolic agents have allowed the operator to be able to reach vessels of extremely small caliber located in deep cerebral structures.

Traditionally, authors have reported variability in overall complication rates (10% to 50% neurological deficit, 1% to 4% mortality). Recently, Haw et al reviewed their experience on 306 patients who underwent 513 embolization sessions.[68] The mortality rate was 2.6% and the morbidity was 4.9%. The location of the AVM in an eloquent part of the brain, presence of a larger fistula, and a venous deposition of liquid embolic agent were related to complications. A clinically important reduction in the rate of death and disabling morbidity occurred in the second half of the study period. Similarly, Ledezema et al performed a single-center, retrospective, nonrandomized study of AVM embolization.[69] Over an 11-year period, 295 embolization procedures (761 pedicles embolized) were performed in 168 patients with embolization as the primary treatment modality (n=16) or as an adjunct to surgery (n=124) or radiosurgery (n=28). There were a total of 27 complications, of which 11 were clinically significant. Excellent or good outcomes (Glasgow Outcome Scale ≥4) were observed in 152 (90.5%) patients. Unfavorable outcomes (Glasgow Outcome Scale 1 to 3) were 3.0% at discharge with a 1.2% embolization-related mortality. Predictors of unfavorable outcome by univariate analysis were (1) deep venous drainage ($P<0.05$), (2) Spetzler-Martin Grade III to V ($P<0.05$), and (3) periprocedural hemorrhage ($P<0.0001$).

Most authors report complete AVM obliteration rates after embolization alone of between 5% and 18%.[70–73] Operator's experience and the improvement in microcatheters, microwires, and embolization materials have made endovascular embolization safer and more effective with regards to permanent and complete obliteration of the AVM. Valavanis and Yasargil reported rates of complete AVM obliteration of 39% in 387 patients. In the subgroup analysis of 182 AVMs that were treated with intent-to-cure they reported a cure rate of 75%.[72] Similarly, Yu et al reported achieving complete obliteration rates of 60% in patients treated with embolization alone.[73]

The embolic agents currently used for the treatment of AVMs include detachable coils, particles such as PVA (polyvinyl alcohol), and liquid agents such as n-butyl cyanoacrylate (n-BCA) and ethylene-vinyl alcohol copolymer. Detachable coils have also been used in the obliteration of AV fistulae and to decrease flow in AVMs in preparation for liquid embolic agents.[63–66,67] Some investigators have also proposed the use of high-concentrated ethanol.[74]

Polyvinyl Alcohol

PVA particles are thrombogenic when infused into small arteries. They are available in different diameters, as per the selection of the operator based on the target vessels.[75–78] The embolization of AVM with particles alone presents several issues.[77–80] The process of nidus occlusion is slower with PVA particles as compared with liquid embolic agents. In addition, during embolization with particles, low-pressure shunts are occluded first with an increase in pressure in the still patent nidal vessels and feeders. The increased pressure in the AVM feeders before they are completely obliterated can increase the immediate risk of hemorrhage. Once AVMs are embolized with PVA particles alone, recanalization rates are usually high. Sorimachi et al reported a 43% rate of nidal recanalization after embolization with PVA.[79] Mathis et al reported a 12% recanalization rate for AVMs embolized with PVA in preparation for radiosurgery.[80] Recanalization is possibly secondary to the development of collaterals because of proximal occlusion, particularly with larger-sized particles.[75–78] For these reasons, AVM embolization with PVA is currently performed mostly to reduce AVM flow in preparation for surgery.

n-Butyl Cyanoacrylate

n-BCA is an adhesive liquid monomeric agent that in contact with a solution containing anions (ie, hydroxyl groups in blood) quickly polymerizes and becomes solid.[81] Such process causes occlusion, marked inflammatory endothelial response, and ultimately, fibrosis.[82] The safety of n-BCA in AVM embolization was tested in a prospective, randomized, noninferiority trial on 114 patients.[78] The authors showed that

n-BCA was equivalent to PVA as a preoperative embolic agent in achieving the prospective volume embolization goal target (79.4% in the n-BCA group and 86.9% in the PVA group) and in reducing the number of vessels embolized (2.2 in the n-BCA group and 2.1 in the PVA group). Because n-BCA can achieve permanent obliteration, it has become the most commonly used liquid embolic agent in the treatment of AVM or AV fistulae of brain and spine.[69,70,73,78,82–84] The viscosity and timing of n-BCA polymerization are the main limiting factors in achieving appropriate nidal occlusion. Decreasing the amount of ethiodol in the mixture can reduce viscosity. For deeper and more homogenous nidal penetration a lower viscous mixture is recommended. To maintain a delayed polymerization, changes in the pH of the solution are recommended.[83,84] The disadvantages of n-BCA are the following: (1) proper delivery of the agent into the nidus requires accurate polymerization time; (2) prolonged injections are difficult; therefore, only a limited amount of nidal vessels can usually be occluded with a single injection; and (3) because n-BCA is adhesive, catheter retention is a possible risk.[78,82–84]

Ethylene-vinyl Alcohol Copolymer

Ethylene-vinyl alcohol copolymer (EVOH) and dimethyl sulfoxide (DMSO) is a nonadhesive solution developed for the treatment of AVM and arteriovenous fistula.[85,86] In Onyx (EV3), EVOH is formed of 48 mol/L ethylene and 52 mol/L vinyl alcohol.[87] The polymer is dissolved in DMSO and is prepared in different concentrations. Micronized tantalum powder (35% weight/volume) is added for radiopacity. The lower the concentration of the copolymer, the less viscous the agent, the more distal is the penetration of the mixture. Jahan et al in a phase I study reported their experience embolizing 129 feeding arteries in 33 procedures on 23 patients.[87] The authors showed an average 63% reduction in AVM volume with the use of Onyx. Two patients experienced ischemia because of the inadvertent occlusion of a feeder. One made a full recovery, and the other had a permanent deficit. Because of its nonadhesive nature, Onyx offers some advantages: (1) long and controlled infusion of the agent can be performed, consequently a large section of the nidus can be potentially embolized with a single feeder injection; and (2) cerebral angiography can be obtained in-between Onyx infusion. The operator can therefore monitor the degree of nidal occlusion and assess the state of the draining veins.[87] The disadvantages of Onyx include the following: (1) DMSO can be potentially angiotoxic, in particular with rapid injection[86–88]; (2) DMSO volume and injection time need to be monitored closely to achieve a safe embolization of AVMs; (3) only catheters that are DMSO-compatible can be used with Onyx; and (4) visibility can be limited in smaller feeding pedicles attributable to the separation of Onyx and the added opacifying agent Tantalum.[86,87] Although Onyx is nonadhesive, only partial reflux can be allowed around the catheter tip because it may still make catheter withdrawal difficult.[87]

Controlled randomized studies are currently underway to compare safety and efficacy of the different liquid embolic materials.

Conclusions

The permanent and safe obliteration of cerebral aneurysms and AVMs is the main goal of any treatment. Endovascular embolization offers a new, minimally invasive approach to these lesions. The technology available to the endovascular operators is rapidly improving, as outlined by this review. The clinical trials that are either underway or in the design stage will be challenged by the fast advancement of the technology and materials available to the operators. Nevertheless, clinical trials are needed as endovascular management continues to develop and advance as a powerful treatment option for cerebral aneurysms and AVMs.

Disclosures

Dr Wakhloo is a consultant for Cordis Neurovascular and EV3 (in 2006 he has received compensation for >$10 000).

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