

DEVELOPMENTS IN EMBOLIC AGENTS FOR BRAIN ARTERIOVENOUS MALFORMATIONS

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Brain arteriovenous malformations (BAVMs) consist of tangles of vessels of different wall thickness and diameter associated with arteriovenous shunting. In BAVMs arterioles and venules communicate directly without the interposition of a capillary bed. BAVMs are relatively uncommon but can cause serious neurological symptoms or death. They are an increasingly recognized entity because of improvements in imaging diagnosis. Approximately ninety percent of BAVMs are located in the supratentorial compartment.¹ The incidence and prevalence of intracranial BAVMs are variable. Annual incidence of symptomatic BAVMs was reported to be 1.1 per 100,000 population.² They often have associated aneurysms.³

Intractable headache, seizures, and progressive neurological deficit are common symptoms. On imaging, intracranial hemorrhage and hydrocephalus are common findings.⁴⁻⁶ Hemorrhage may be related to an associated aneurysm.⁷ Incidence of hemorrhage from an unruptured BAVM is about 2% to 4% per year. Compared with computed tomography (CT), magnetic resonance imaging (MRI) has a higher sensitivity for the diagnosis of BAVMs.^{8,9} On MRI the lesions appear as homogeneous signal voids on T1 and T2 weighted sequences. Arteriography is the 'gold standard' for defining the arterial and venous anatomy. Typical findings on arteriography are hypertrophied arteries leading to the lesion and hypertrophied veins draining from it, their size depending on the size of the shunt present. Both arteries and veins fill rapidly, prior to contrast medium passing through the normal capillary phase in the adjacent tissue.

Spetzler and Martin¹⁰ have proposed a grading scale to predict surgical outcome. This instrument has also been evaluated in the combined management of BAVMs involving surgical resection, surgery plus embolization, embolization alone, or radio-surgery in various combinations with other modalities.¹¹ The grading scale assigns points based on the size of the BAVM, the

eloquence of the surrounding brain (eloquent brain regions are defined as those that, when disrupted, yield a readily identifiable neurologic deficit), and the pattern of venous drainage. The risk of morbidity and mortality rises steadily with increasing grade. The system is outlined in Table 1.

Table 1: Grading of Arteriovenous Malformations

Graded Feature	Points Assigned
Size of arteriovenous malformation	
Small (< 3cm)	1
Medium (3 - 6 cm)	2
Large (> 6cm)	3
Eloquence of surrounding brain	
Non-eloquent	0
Eloquent	1
Pattern of venous drainage	
Superficial only	0
Deep	1

From ref. 10.

Score 1 corresponds to grade I (mildest)
 Score 2 corresponds to grade II
 Score 3 corresponds to grade III
 Score 4 corresponds to grade IV
 Score 5 corresponds to grade V (severest)
 Inoperable lesions are grade VI

Recommendation for endovascular management of BAVMs have traditionally been divided into pre-surgical, pre-radio-surgical, or palliative management for focal neurological symptoms or uncontrolled seizures. However, recent developments have led to a more aggressive application of endovascular treatment as the sole therapy in appropriate lesions.

Surgical extirpation used to be considered the primary mode of therapy for Spetzler-Martin grade I and II lesions; however, these lesions are now also being treated with embolization. Radio-surgery can be considered in lesions thought to be at high risk from a surgical or endovascular standpoint (usually because of location or feeding vessel anatomy). Spetzler-Martin grade II and III lesions may be embolized before surgery or radio-surgery. Grade IV and V lesions should not be embolized unless this is to be done in conjunction with other treatment modalities (surgery or radio-surgery) with the goal of complete care.¹²

The embolization is performed under general anesthesia. Vascular access is obtained through one of the femoral arteries in the groin. A guide catheter is placed in the internal carotid artery and a micro-catheter is then advanced into the intracranial vessels, eventually to be positioned within the nidus of the AVM or at the entrance of a fistula. A super-selective angiogram is then obtained to evaluate flow characteristics, angiographic architecture, and venous outflow, prior to the deployment of embolic agents.¹³

EMBOLIZATION MATERIALS

Initial experiments in endovascular management of BAVMs were largely unsuccessful as the agents used resulted either in very proximal occlusion (Gelfoam), leading to rapid development of collaterals; or damaged normal brain tissue (Absolute Alcohol), leading to unacceptable side effects. Although a very large range of materials has been used to try and embolize BAVMs, it was the introduction of acrylate adhesive (more popularly known as Superglue) agents that have had the most impact. Lately Onyx, a new agent, has allowed the treatment of lesion previously considered untouchable.

Cyanoacrylates

Acrylate-based glues are now the mainstay of BAVM embolization. Histoacryl (N-Butyl-2-cyanoacrylate) is a liquid which when exposed to ionic solutions results in rapid polymerization. Polymerization converts the liquid to a solid. When injected into a vessel, this causes permanent and irreversible thrombosis. The rate of polymerization can be slowed by the addition of iophendylate or glacial acetic acid; additional opacification can be achieved by the addition of tantalum or bismuth powder. The speed of polymerization is controlled by the addition of ethidiol. Before injecting glue, the catheter must be flushed with dextrose water to prevent polymerization within the catheter. Polymerization is accompanied by heat production, which may lead to a degree of angioneurosis. The risks associated with the use of these agents include

stroke or cranial nerve dysfunction due to occlusion of branches other than the desired branches, obstruction of venous outflow, and cementing of catheter in the vessel.¹⁴⁻¹⁶ Due to rapid polymerization, usually only one compartment of the AVM can be embolized at a time. The injection has to be continuous and relatively short as prolonged injection results in cementing the catheter in place.

Given the somewhat unpredictable polymerization behavior of N-butyl-2-cyanoacrylate, there was a need for an agent that would combine effective thrombosis with predictable deployment. Neuracryl (2-hexyl cyanoacrylate) has these properties. The solution is prepared by mixing 2-hexyl cyanoacrylate monomer with a thick yellowish brown mixture of 2-hexyl cyanoacrylate polymer, gold powder, and fatty acid. This is a single viscosity agent, with less adhesiveness but more viscosity than N-butyl-2-cyanoacrylate. The catheter can be withdrawn even after it has partially hardened.^{17,18} Although this agent has a better side-effect profile, it is also more expensive.

Cyanoacrylates result in permanent occlusion of the vessels; however, they also cause the vessel wall to harden and become brittle. This makes subsequent surgical intervention technically challenging.

Onyx

Onyx is a new embolization material that has recently become commercially available, although its main component has been in use since the 1990s. Onyx is composed of ethylene-vinyl alcohol copolymer (EVOH) with dimethyl-sulfoxide (DMSO) solvent. Tantalum powder is added to the mixture for radiopacity. It is available in three forms - Onyx 18, Onyx 20 and Onyx 34. Onyx 18 contains 6% EVOH and 94% DMSO, Onyx 20 contains 6.5% EVOH and 93.5% DMSO, and Onyx 34 contains 8% EVOH and 92% DMSO. These varying proportions result in different viscosities, allowing the selection of the most appropriate one depending on the anatomy of the lesion being treated. Onyx is a non-adhesive, non-absorbable embolic agent with soft flow patterns causing permanent occlusion of vessels. It forms a soft, sponge-like mass that is easy to handle during surgery. Treated vessels are less fragile and less likely to bleed during surgery. These changes are largely because of a lower level of inflammatory reaction and absence of polymerization heat compared to cyanoacrylates. Akin et al¹⁹ found less intra-operative blood loss and a shorter duration of surgical procedures for lesions embolized with Onyx compared with N-butyl-2-cyanoacrylate in an animal model.

Several compartments of the BAVM nidus can be embolized from a single catheter position. Because of the

non-adhesive properties of Onyx, the injection can be interrupted to assess the progress of the embolization and can then be continued. As an embolization agent, Onyx's overall use is significantly easier and the behavior more predictable when compared with cyanoacrylates. Although removal of the micro-catheter is no longer a problem with Onyx, venous occlusion and subsequent haemorrhage may occur after embolization.²⁰⁻²⁷

Polyvinyl Alcohol Particles (PVA)

Polyvinyl alcohol particles occlude small arteries and arterioles. Although the mechanical occlusion along with inflammatory reaction within the vessel wall leads to permanent occlusion, re-canalization has been described. The risk of re-canalization remains a significant draw back in the use of PVA as a primary embolic agent. PVA particles are available in a variety of sizes ranging from 50 to 2500 μ m in diameter. Dilute suspensions of small particles (< 700 μ m) pass easily through most micro-catheters. PVA is radiolucent, therefore it must be mixed with contrast for delivery. Small particles should not be used if a substantial degree of arteriovenous shunting is suspected.^{28,29}

Coils

Metallic coils are manufactured from various materials such as stainless steel, tungsten, and platinum. Platinum coils have the advantage of being magnetic resonance (MR) compatible and highly visible fluoroscopically. Although coils produce permanent occlusion, coil embolization in the context of BAVMs should be considered a temporary measure as recruitment of abundant new feeders occurs rapidly. A definitive procedure, which is usually surgery, should be performed within one to two days. Coil embolization of proximal feeders of an AVM can have a favorable outcome on surgery without risking ischemic damage to normal structures. An innovative form of coil is the so-called liquid coil, which is made from extremely fine platinum wire and is thus very flexible. Liquid coils are intended to be flow-directed. Their primary application is in the treatment of BAVMs in combination with cyanoacrylates, and they are used to reduce the flow rate through the BAVM before embolization with glue. The glue is then deposited on the liquid coil matrix.

COMPLICATIONS

Minor transient ischemic attacks are reported, with an observed frequency of approximately 1% - 15%. The incidence of major complications is not well documented. Major complications include retrograde thrombosis of the longer trunk which supplies the BAVM, as well as small branches of normal brain; non-target occlusion which is

probably more common than realized and usually associated with particulate embolization;²⁸ peri-embolic inflammation, which may require steroids but is rarely seen with the new agents; and normal perfusion pressure breakthrough,^{30,31} which occurs when the high flow shunt of the BAVM is occluded and nearby normal brain and its capillary bed are exposed to normal perfusion pressure, resulting in edema formation and hemorrhage. Distal venous thrombosis^{32,33} is also a major complication and can cause pulmonary emboli. Vascular perforations are usually associated with micro-wire use or manipulation of catheters.^{34,35}

CONCLUSION

Endovascular therapy for BAVMs is now employed widely with high degrees of success and relatively infrequent complications. This has been made possible by the introduction of safer, more predictable embolic agents which allow targeted delivery to the nidus. Potentially, the most exciting new development is Onyx, although its use in developing countries such as Pakistan is impeded by its high cost.

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