Embolic materials for cerebral endovascular theraphy

Al. Chiriac[1], Jorg Baldof[2], N. Dobrin[3], I. Poeata[1]

[1]"Gr.T. Popa" University of Medicine and Pharmacy Iasi, Romania
[2]Ernst-Moritz-Arndt-University of Greifswald, Germany
[3]"Prof. Dr. Nicolaie Oblu" Clinical Hospital Iasi, Romania

Abstract

Cerebral embolization is one of the most important procedures in neuroendovasculare intervention. Fast developments of new microcatheters that can be maneuvered endovascularly into the brain have permitted the treatment of lesions without conventional neurosurgery. Also, the progress in biomaterial science has contributed significantly to the development of this new therapeutic modality.

Various embolic materials in clinical use are reviewed, such as cyanoacrylates, ethylene-vinyl alcohol copolymer mixtures, Ethibloc, ethanol, estrogen, poly(vinyl acetate), cellulose acetate polymer, poly(vinyl alcohol), gelatin sponges, microfibrillar collagen, surgical silk sutures, detachable balloons, and coils. These materials are reviewed in the context of treatment application for various brain lesions, such as arteriovenous malformations, cerebral aneurysms, and head and neck tumors. Further developments in biomaterial polymer science can bring about progress against brain diseases.

Keywords: aneurysm, arteriovenous malformation, cerebral embolization, coils, embolic materials

Introduction

Cerebral embolization is defined as the "therapeutic introduction of various medical substances or devices into the brain circulation to occlude vessels or other vascular anomalies (aneurysms), either to arrest or prevent hemorrhaging; to devitalize a structure such as tumors, or to occlude its blood supply; to reduce blood flow to an arteriovenous malformation; to remodel a vascular wall or for a blood flow redirectionation. The procedure can be used as a single clinical therapy or in combination with other neurosurgical therapies (microsurgical resection or radiotherapy).

Embolization, or embolotherapy, is performed in a special dedicated laboratory by neurosurgeons or neuroradiologists who have completed advanced postresidency training (fellowship) in neuroendovasculare intervention.

After inserting a catheter into the target vessel, it is carried out by injecting or placing embolization materials via the catheter. Indications for arterial embolization include devascularization of tumors, control of hemorrhage, occlusion of arteriovenous malformation or aneurysms, ablation of an epileptic region, and redistribution of blood flow. Various embolization materials have been developed

and used in accordance with these purposes.

Embolization materials clinically used are; metallic-coils, micro-coils, gelatin sponges, starch microspheres, auto-agglutinated blood, dehydrated ethanol, NBCA, IBCA, lipiodol, embospheres, SAP-MS, PVA, pluronic and gelatin particles. The choice of embolization material usually depends on the diameter of the vessel to be embolized and the expected duration of the embolic effect. Embolization of large, central vessels usually requires mechanical devices such as metallic coils or detachable balloons and particulate or liquid materials are required for small vessels close to the capillaries. In this exhibit, we will classify these materials into four types; mechanical devices, particulate, liquid agents and sclerosant agents and review these proper indications, uses and mechanisms of action. Some experimental results of newly developed embolization materials will be also shown.

The materials are categorized as particulate, liquid, and mechanical in form, and as temporary and permanent in durability. The choice of embolization material depends on the size of the artery to be occluded and the duration of occlusion desired. The physical properties of embolization materials also should be considered.

Embolization may have 3 therapeutic goals:

1. An adjunctive goal (eg, preoperative, adjunct to chemotherapy or radiation therapy)

2. A curative goal (eg, definitive treatment such as that performed in cases of aneurysms, arteriovenous fistulae [AVFs], arteriovenous malformations [AVMs], and traumatic bleeding)

3. A palliative goal (eg, relieving symptoms, such as those of a large AVM, which cannot be cured by using embolotherapy alone)

Medical conditions treated by using embolotherapy can be grouped as follows:

1. Vascular anomalies (eg, AVM, AVF, venous malformation [VM], lymphatic malformation [LM], and hemangioma)

2. Hemorrhage (eg, pseudoaneurysms and GI tract, pelvic, posttraumatic, epistaxis, and hemoptysis bleeding)

3. Other conditions (eg, tumors, varicoceles, and organ ablation)

Embolic agents

Mechanical Devices

Coils

Endovascular coiling was introduced by Italian interventional neuroradiologist Dr. Guido Guglielmi at UCLA in 1991. It consists of passing a catheter into the femoral artery in the groin, through the aorta, into the brain arteries, and finally into the aneurysm itself. Once the catheter is in the aneurysm, platinum coils are pushed into the aneurysm and released.nA Guglielmi Detachable Coil, or GDC, is a platinum coil commonly used in intracranial non-invasive surgery for the occlusion of brain aneurysms. Guglielmi in 1990, and was gradually introduced in the later 1990s as an alternative to surgical clipping, which requires invasive surgery. The GDC system consists of a soft platinum coil soldered to a stainless steel delivery wire. When the coil is properly positioned within the fundus a 1 mA current is applied to the delivery wire. The current dissolves the stainless steel delivery wire proximal to the platinum coil by means of electrolysis. At the same time, the positively charged platinum theoretically

attracts the negatively charged blood elements such as white and red blood cells, platelets, and fibrinogen thus inducing intra-aneurysmal thrombosis. Once electrolysis occurs the delivery wire can be removed leaving the coil in place. Mechanically and electronically detachable coils are currently available.

The ball coils initiate a clotting or thrombotic reaction within the aneurysm that, if successful, will block the blood flow into the aneurysm and preventing rupture. In the case of broad-based aneurysms, a stent is passed first into the parent artery to serve as a scaffold for the coils ("stent-assisted coiling").

Coils are made from stainless steel, platinum, or titanium wire to be visible via X-ray and be flexible enough to conform to the aneurysm shape. Most are coated with Dacron fibers to elicit greater thrombogenic reactions. Coils are made of soft platinum wire smaller than a strand of hair and are available in different diameters and lengths. All detachable coils are scientifically proven to be safe and effective.

There are four types of coils (Figure 1):

- bare platinum coils
- coated platinum coils
- biologically active coils.
- radioactive coils

The peculiarities of bare platinum coils lie in its physical as well as its electrolytical properties: The material has a high memory effect, allowing it to easily bend and regain its original coil shape. It is also highly sensitive to low currents, which allow the detach from the catheter that carries it, thus receiving the name of "detachable coil".

Coils can be grouped into microcoils and macrocoils. Microcoils (platinum coils) can be delivered through microcatheters (2.2-3.5F). They can be particularly useful when superselective coil embolization is required. Microcoils are highly thrombogenic, radiopaque, and biocompatible. Collateralization is a potential disadvantage of coil embolization, and it can result in the persistence of flow into the vascular territory of the vessel that was embolized with the coil. Additionally, when proximal occlusion occurs with coil embolization, repeat intervention via the same artery becomes difficult, if not impossible. The most used bare platinum coils system used today are GDC coils from Boston Scientific, Micrus Coils and Trufill DCS Orbit Detachable Coil System from Codman Neurovascular.

Macrocoils, also called, were first introduced in 1975. Coils have the advantage of being precisely positioned under fluoroscopic control. To increase the thrombogenic effect, Dacron wool tails are attached to coils. The coils are available in many sizes and may be delivered through commonly used angiographic catheters (4-5F).

Again, the thrombogenic effect primarily results from the addition of silk or synthetic fibers, not from the coil.

Hydrogel-coated coil (HydroCoil Embolic System, MicroVention, Aliso Viejo, Calif) is one of the biologically active detachable coils that were developed to achieve more durable aneurysm occlusion by improved volumetric percentage occlusion of the aneurysmal cavity. The HydroCoil Embolic System (MicroVention) is a recently developed coil technology designed to improve packing density. Hydrogel-coated coils (HydroCoils) consist of platinum coils covered with a hydrophilic polymer that swells in blood.

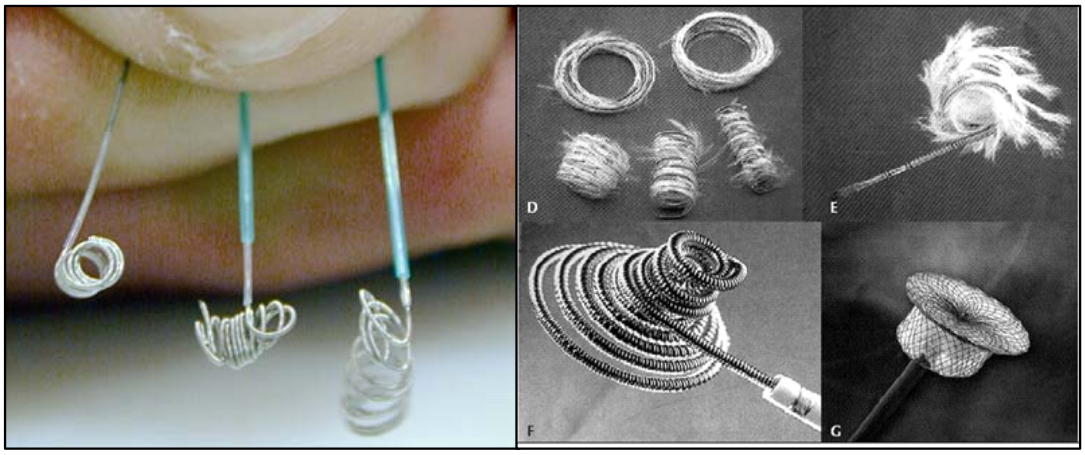


Figure 1 A, B, C GDC Coils System; D: Coils de Gianturco; E: Flipper Detachable Coil; F: Nit-Occlud; G: Amplatzer Duct Occlud

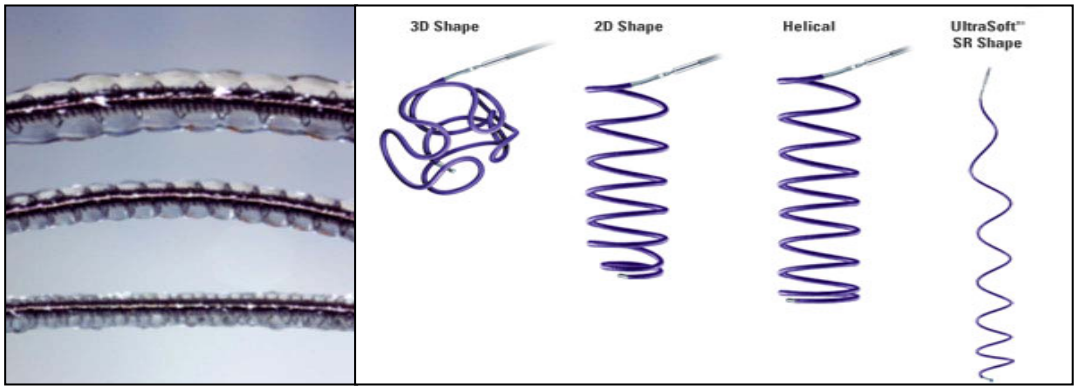


Figure 2 A HydroCoil Embolic System; B- Matrix Coils

Coil swelling in vivo should theoretically result in greater aneurysm filling compared with inert platinum coils and may translate into more durable therapy (Figure 2A).

Matrix Coils are platinum coils covered with an absorbable copolymer. They employ a proprietary outer copolymer coil over an inner platinum main coil. The copolymer runs the entire length of the main coil and constitutes approximately 70% of total coil volume. The absorbable copolymer is typically absorbed by the body within 90 days. Matrix Coils employ a well-characterized Polyglycolic-Polylactic Acid (PGLA) copolymer that has been used in many biocompatible devices, such as surgical staples, orthopedic implants, sutures, and drug delivery vehicles. Matrix Coils utilize electrolytic detachment for coil delivery. Because the electrolytic process does not rely on mechanical movement to deliver the coil, it provides precise, motion-free detachment. Matrix Coils (Figure 2B).

Stents

An endovascular stent graft is a tube composed of fabric supported by a metal mesh called a stent. It can be used for a variety of conditions involving the blood vessels, but in neurosurgery most

commonly is used to reinforce a weak spot in an artery (an aneurysm) or to re-establish the blood flow throw a stenosed vessel (Figure 3). The stent graft is designed to seal tightly with your artery above and below the aneurysm. The graft is stronger than the weakened artery and it allows your blood to pass through it without pushing on the bulge.

Brain aneurysm stenting is performed when wide-necked brain aneurysms are treated with endovascular coils. Wide-necked aneurysms are characterized by a large opening to the blood vessel on which they formed. The large opening makes these aneurysms prone to coil herniation, or displacement of coils from the aneurysm into the parent blood vessel. Coil herniation may cause serious complications. Stents are small, flexible, tube-like devices. A stent is placed across the aneurysm neck to keep coils inside the wide-necked brain aneurysm during treatment. In this procedure, the stent is intended to help hold the coils within the aneurysm to prevent coil herniation. So, after stent placement another catheter is then navigated through the deployed stent the aneurysm. Tiny platinum coils are threaded through the catheter and deployed into the aneurysm, blocking blood flow into the aneurysm and preventing rupture (Figure 4 A, B).

The severe clinical vasospasm due to aneurysmal subarachnoid haemorrhage or endovacular catheter and coil manipulation remains a great chaleange for neurointerventionist specialists. However, transluminal balloon angioplasty and the intraarterial stent placement represent successful tools in treating severe refractory cerebral vasospasm.

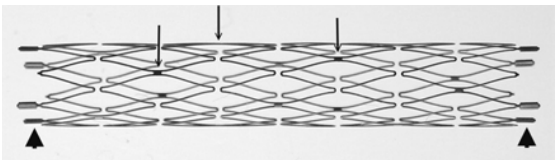
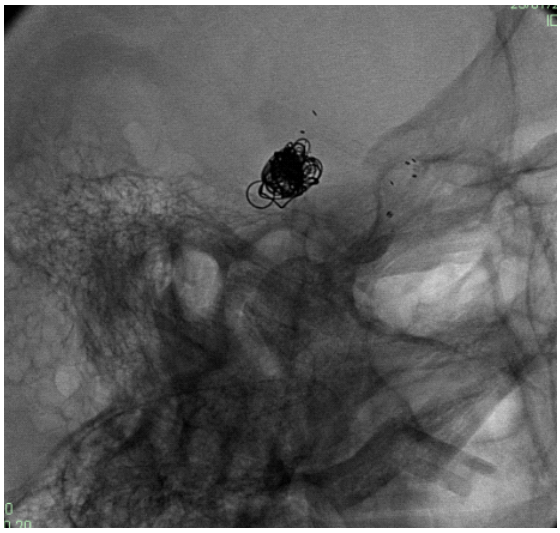


Figure 3 Image of a stent with Rx markers (big arrow) and connection points (small arrow)



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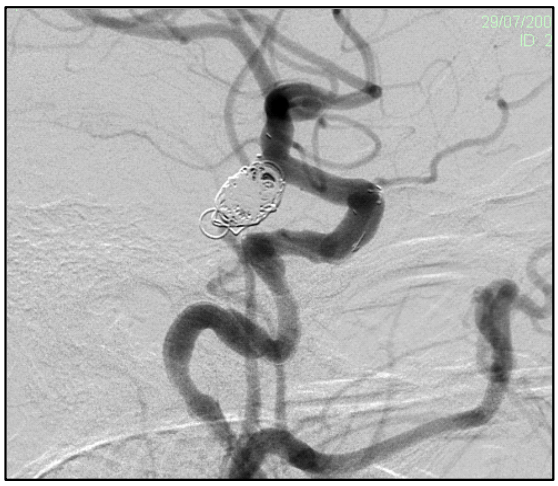


B

Figure 4 Angiografic image of an PComA aneurysm embolized by stent and coil technique (A-with and B-with out contrast enhancement)

Several clinical studies report also, the successful treatment of acute sinus thrombosis by sinus angioplasty with stent deployment.

The Neuroform stent is the first microcatheter-delivered stent designed specifically for the neuroendovascular treatment. The stent functions primarily to provide durable parent vessel protection during the embolization of broad-necked cerebral aneurysms. Neuroform3 Stents employ a highly flexible, hybrid cell design for better tracking during access and greater conformability within a variety of vessel morphologies. The Neuroform3 hybrid cell design is engineered to provide greater scaffolding for coil mass support and sufficient radial force to generate stability within the vessel.

Baloon occlusion

The concept of a catheter-delivered detachable balloon as a therapeutic cerebrovascular device is credited to Serbinenko. In North America, the technique (in various permutations) has been popularized by Debrun et al and Heishima et al for the treatment of direct carotid cavernous fistulas (CCFs) and by others for hunterian occlusion (after successful test occlusion) of giant, intracranial aneurysms(Figure 5).

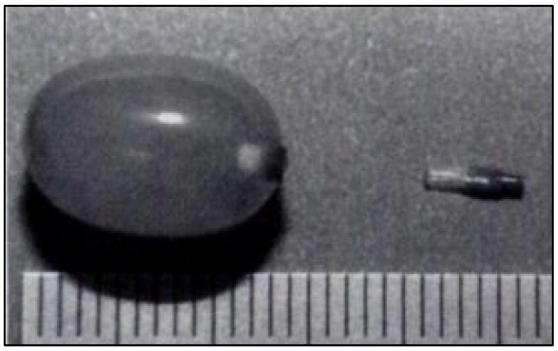
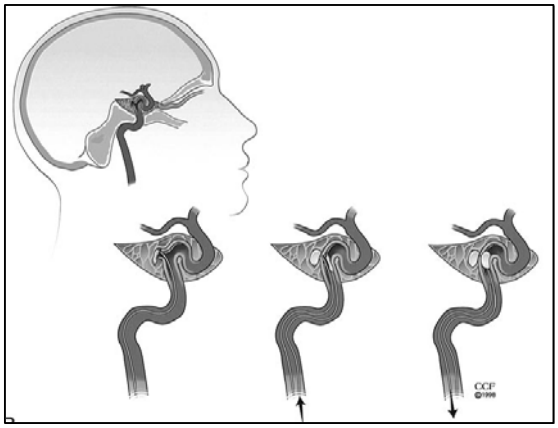


Figure 5 Detachable balloon inflated and deflated

The detachable balloon catheter is comprised of latex detachable balloons having a hollow cylinder securely fastened at the neck or entrance to the balloon. A catheter tube is held inside the cylinder by a releasable retainer which permits atraumatic detachment of the catheter tube after placement of the balloon in a lesion. A seal means is installed inside the balloon for sealing the balloon after its placement and inflation. The releasable retainer permits atraumatic detachment by complete separation of the catheter tube from the balloon and its withdrawal after placement of the balloon without any force being applied to the arterial lesion.

Detachable balloon occlusion may provide an alternative therapy for selected cases of direct arteriovenouse fistulas or difficult aneurysms. Under fluoroscopic visualization, a silicone balloon is flow-directed through the intracranial circulation and guided directly into the aneurysm or region of aberrant connection between artery and vein. Using real-time subtraction or "road mapping" techniques, the balloon is inflated with a enhancement solution, hydrophilic polymer, hydroxyethyl methacrylate, which solidifies to create a permanent embolic agent. The balloon is then detached within the fistula or aneurysm, and angiography is done to confirm occlusion of the aneurysm with preservation of the parent artery (Figure 6A).

Ectatic aneurysms without a neck may be treated by occluding the aneurysm or the parent artery (or both). The procedures are done from a transfemoral approach using local anesthesia to permit continuous neurologic monitoring of the patient's condition.



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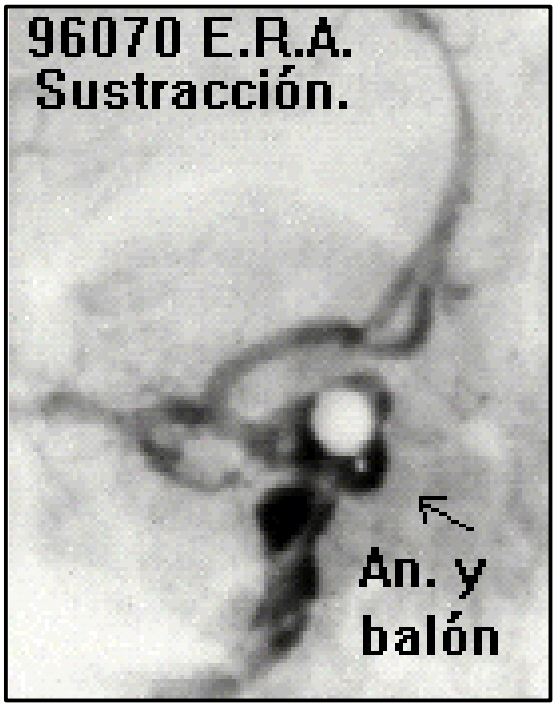


B

Figure 6 A Grafic of a CCF balloon embolization, **B** Angiografy of ICA aneurysm treated by ballon embolization

The technique has been used to treat aneurysms of the proximal, mid, and distal basilar, posterior cerebral, lateral posterior choroidal, cavernous internal carotid, posterior communicating, carotid ophthalmic, carotid bifurcation, and middle cerebral arteries(Figure 6B).

Although generally accepted as the method of choice for the treatment of direct CCFs, detachable balloon embolization in the CNS is a procedure of some complexity, with a potential for significant complications. Many factors influencing outcome bear on the critical timing of balloon detachment. Previous reports have emphasized detachment of these devices by means of a second, coaxial (4F over 2F) sleeve, which pushes the balloon off the delivery catheter, or by means of simple inflation and gentle traction on the delivery catheter (3). Poor tracking of the sleeve and inability to push the balloon into place may hamper the former method. The second technique is fraught with the risk of balloon migration (particularly into the carotid artery) at the time of detachment.

Particulate

Polyvinyl alcohol

PVA is obtained by the reticulation of PVA (Ivalon) with formaldehyde. PVA is available as particles with a large range of sizes. For sizes as large as 710 μ m, a microcatheter can be used as a delivery catheter (Figure 7).

Successful PVA-particle embolization depends on the formation of a thrombus in which a large proportion of the embolized vessel is filled with thrombus rather than PVA particles. Histologically, this agent causes intraluminal thrombosis associated with an inflammatory reaction, with subsequent organization of the thrombus. PVA is considered a permanent embolic agent because of the low frequency of recanalization of the embolized vessels. PVA is not absorbable, and it likely produces permanent occlusion.

Figure 7 CONTOUR microparticle for cerebral embolization

PVA is usually administered in a mixture of contrast medium and isotonic sodium chloride solution under fluoroscopic guidance. Aggregation of PVA particles can be minimized by using dilute contrast medium in a matched-density suspension; for example, Omnipaque and sodium chloride solution can be used in a ratio of 1:0.4 for contour particle suspension. PVA particles have a tendency to aggregate within the vessel once administered, potentially leading to an occlusion that is more proximal than intended. Diluted mixtures advance more distally, whereas concentrated mixtures cause more proximal occlusions.

Tris-acryl gelatin microspheres

Microspheres (Embosphere; Biosphere Medical, Rockland, Mass) are biocompatible, hydrophilic, nonresorbable, and precisely calibrated particles produced from an acrylic polymer and impregnated with porcine gelatin. Microspheres are available in sizes of 40-1200 μm, and they are supplied in apyrogenic sterile sodium chloride solution.

To provide the desired clinical outcome, appropriately sized microspheres and delivery catheters must be chosen to best match the size of the target vessel. For example, when AVMs are being embolized, choose a particle size that occludes the nidus without passing into the systemic circulation. These particles typically do not aggregate, and this is a distinct advantage of microspheres compared with PVA particles.

Microspheres can tolerate temporary compression of 20-30% to facilitate their passage through the delivery catheter. When a coaxial technique is used, a 2.5-3.0F microcatheter allows the passage of microspheres as large as 700 μm for embolization.

Because microspheres are not radiopaque, contrast enhancement must be used to monitor embolization under fluoroscopic guidance. Microspheres are considered permanent embolic particles.

Gelfoam

Gelfoam is a sterile gelatin sponge intended for application to bleeding surfaces for hemostasis or for use as a temporary intravascular embolic material. It is a water-insoluble, off-white, nonelastic, porous, and pliable material. Gelfoam may be cut without fraying, and it can absorb and hold many times its weight in blood and other fluids.

Gelfoam is usually absorbed completely (depending on the amount used, degree of saturation with blood, and site at which it is used), with little tissue reaction. When used as an embolic material, the vessel recanalizes within a few weeks. Gelfoam is supplied in a sterile envelope enclosed in an outer peelable envelope. It is available in sizes from 12 mm to 6 cm.

Liquid Agents

Cyanoacrylate

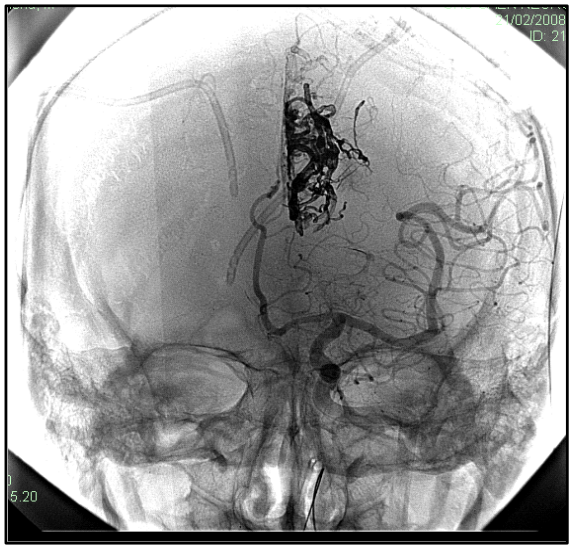
Cyanoacrylate, or N- -butyl-2-cyanoacrylate (NBCA) is a rapidly hardening liquid adhesive often referred to

as glue. The substance hardens (polymerizes) immediately on contact with blood or other ionic fluid. Polymerization results in an exothermic reaction that destroys the vessel wall (Figure 8).

Penetration of the capillary bed causes severe tissue injury. Because of the rapid polymerization, coaxial catheterization, precise positioning of the delivery catheter and considerable skill are required for NBCA embolization. When a suitable location is reached by using a microcatheter, the catheter is flushed with 5% dextrose to clear it of any blood or contrast medium.

Under real-time fluoroscopic control, a mixture of NBCA and oily contrast medium is delivered. As soon as a cast of the vascular tree is seen fluoroscopically, the delivery microcatheter is quickly removed so that the catheter tip does not adhere to the vessel. Again, the catheter is flushed quickly with 50% dextrose so that it can be reused during the same procedure.

Figure 8 GLUBRAN2 the second generation of cyanoacrylate liquid agent



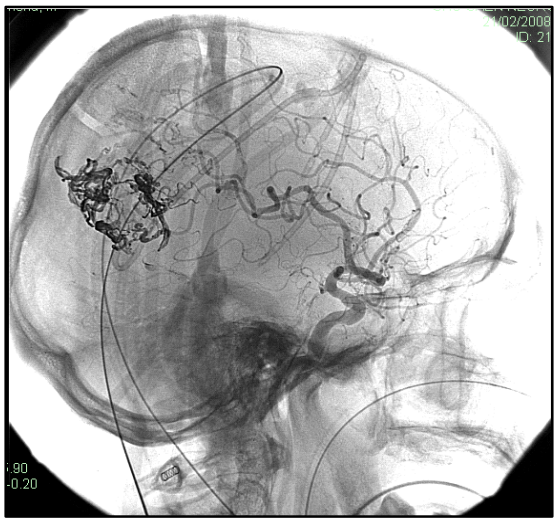


Figure 9 Angiography anterior and lateral view of an occipital AVM embolized with Onyx

Onyx

Onyx ((EVOH) is a bio-compatible liquid polymer that precipitates and solidifies in contact with blood, thus forming a soft and spongy embolus. The application of the ethylene-vinyl alcohol copolymer (EVOH) in the endovascular treatment of intracranial AVMs was first described by Taki et al7 and Terada et al8 in the early 1990s. A mixture of 60 parts of the solvent dimethyl-sulfoxide (DMSO), 5 parts of EVOH, and 35 parts of the contrast agent metrizamide was used. EVOH is now commercially available as the nonadhesive liquid embolic system under the names Onyx 18, Onyx 20, and Onyx 34 (ev3, Irvine, Calif) and is CE-marked for the treatment of intracranial AVMs in Europe.

Since July 2005, Onyx 18 and Onyx 34 have been approved in the United States by the Food and Drug Administration. The numbers 18, 20, and 34 quantify the viscosity of Onyx in centipoises (cp). Onyx 18 contains 6% EVOH and 94% DMSO, Onyx 20 6.5% EVOH and 93.5% DMSO, and Onyx 34 8% EVOH and 92% DMSO. Tantal powder is added to the mixture for radiopacity.

Onyx must therefore be shaken for at least 20 minutes before injection to achieve homogeneous radiopacity of the mixture. DMSO is potentially angiotoxic, but this effect is negligible if used with the recommended infusion rates. If the mixture comes into contact with aqueous solutions, precipitation of the polymer is initiated by diffusion of DMSO. This process begins on the surface while the core is still liquid, resulting in a soft, nonadherent mass. Therefore, Onyx has a lavalike flow pattern within blood vessels without any fragmentation during the injection (Figure9). Due to these properties and because Onyx is not absorbable, it is capable of producing permanent vascular occlusion.11 Once the microcatheter is wedged into the Onyx cast around the tip of catheter, several compartments12 of the nidus can be embolized from a single catheter position. The embolized part of the nidus appears larger than the opacified part during selective contrast agent injections from the microcatheter. Because of the nonadhesive properties of Onyx, the injection can be interrupted to assess the progress of the embolization and can then be continued.

Sclerosant Agents

Ethanol

Ethanol (absolute alcohol) is the most commonly used liquid agent. Embolization with absolute alcohol has a direct toxic effect on the endothelium that activates the coagulation system and causes the microaggregation of red blood cells.

In the treatment of vascular malformations, ethanol has demonstrated its curative potential compared with the palliative effect seen with other embolic agents. Occlusion of the lumen occurs within minutes or days. Ethanol can be damaging if it reaches the capillary bed of any given tissue (eg, skin), and it usually causes significant soft-tissue swelling, which may subsequently cause compartment syndrome (nerve compression).

When absolute alcohol is mixed with a contrast medium and when small catheters are used, superselective vascular embolization can be safely performed under fluoroscopic guidance. Ethiodized oil (Ethiodol), an oily contrast medium, is used most commonly.

If large amounts of absolute alcohol enter the systemic circulation, toxic effects can occur. These include central nervous system (CNS) depression, hemolysis, and cardiac arrest. Slow, careful injections by using balloon occlusion arterial catheters for delivery and by applying manual compression on the draining veins (or tourniquet control) or balloon occlusion of the draining system may decrease alcohol washout from the lesion and reduce acute systemic toxicity. Ethanol 1 mg/kg is the maximum amount that can be injected during a single session.

Sodium tetradecyl sulfate

Sodium tetradecyl sulfate (Sotradecol) is another sclerosant. This contains 2% benzyl alcohol and is commonly used for VMs and varices. Use of this agent is less painful for the patient, and it is considered to be less toxic then absolute alcohol. Therefore, some lesions can be treated without general

anesthesia.

Sodium tetradecyl sulfate can be used as a sclerosant in various concentrations (1-3%); however, manufacture of this agent has been discontinued in the United States. This author has begun using ethanolamine oleate (Ethamolin; Questcor Pharmaceuticals, Hayward, Calif) instead of sodium tetradecyl, with the same indications.

Other materials

Other less commonly or previously used materials include balloons, microfibrillar collagen (Avitene), autologous materials, ethylene vinyl alcohol, alginates, phosphoryl choline, sodium morrhuate, hot contrast material, and 50% dextrose.

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