Arteriovenous malformations of the brain: choosing embolic materials to enhance safety and ease of excision

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The authors report their experience with surgical resection of 108 previously embolized arteriovenous malformations (AVM's). Embolization was performed via only transfemoral catheterization in 70 lesions and via the surgical exposure of feeding vessels in 32. The remaining six patients were referred for resection following silicone sphere embolization elsewhere. Materials used included polyvinyl alcohol (PVA) foam, platinum microcoils, detachable silicone balloons, surgical silk, a mixture of 33% ethanol and microfibrillar collagen, and isobutyl cyanoacrylate (IBCA). It is believed that proximal arterial occlusion with balloons is an inferior choice for preoperative embolization, because the technical difficulty of placement is high and the nidus of the AVM is unaffected. Vascular coagulation and section and AVM retraction are more difficult with IBCA; therefore, this is also considered an inferior choice.

Among the materials studied, the combination of PVA for distal occlusion and microcoils for proximal occlusion appears to be the superior choice. Fewer complications (stroke or hemorrhage) are seen when intrarterial Amytal (amobarbital) testing is used to guide the embolization. Data regarding toxicity, oncogenicity, and vascular metabolism or recanalization associated with PVA, IBCA, and n-butyl cyanoacrylate are reviewed.

KEY WORDS • arteriovenous malformation • cerebrovascular system • cyanoacrylate • embolization • polyvinyl alcohol

In the last decade, the use of embolization of arteriovenous malformations (AVM's) prior to surgical resection has undergone explosive growth. The first catheters that were used intracranially ended in calibrated-leak balloons, necessitating the use of liquid embolic materials; isobutyl cyanoacrylate (IBCA) was the most widely used agent. With the introduction of polyvinyl alcohol (PVA) foam, a new embolic material became available. Manufacturing refinements have now created PVA particles varying in diameter from 150 µ to greater than 2 mm. The additional evolution of detachable balloons, hydroxyethyl methacrylate polymerizing solution, Gelfoam, n-butyl cyanoacrylate (NBCA), ethanol plus microfibrillar collagen material (F Viñuela, et al., unpublished data), surgical silk particles, and platinum microcoils has led to the introduction of a wide array of chemicals and devices that can be injected or inserted into cerebral arteries.

Since embolization is now often performed before surgical resection, it is important to know if one material facilitates surgery more than the others. In this report, we compare the embolic materials with which we have direct surgical experience as to their ease of coagulation, cutting, and retraction. We also review the literature to ascertain whether there exist relative advantages of one material over another with regard to toxicity, mutagenicity, or metabolism.

Clinical Material and Methods

Patient Population
A total of 108 patients with previously embolized AVM's constitute this series, including six patients with malformations who were referred to us following silicone sphere embolization performed elsewhere (Table 1). One of us (P.D.P.) has performed 96 of these embolization procedures in 70 patients, and another (D.S.) has performed an additional 42 intraoperative embolizations in 31 patients using IBCA (some of these cases have been reported previously). Embolization with PVA via a surgically exposed feeder was performed in one case. The embolizations performed via transfemoral catheterization include intracerebral catheriza-
tions selectively into AVM-feeding vessels in 85 procedures in 59 patients. Of these, PVA either alone or in combination with other materials was utilized in all but three procedures. Two of those were performed on a patient undergoing a total of three procedures, with PVA used in the third procedure. Therefore, of the 59 patients undergoing intracerebral catheterizations, PVA was used in 58.

Data Analysis

The 82 embolization procedures performed via selective catheterization of AVM-feeding vessels in 58 patients were analyzed for the occurrence of neurological complications (stroke or cerebral hemorrhage), for the effect of the addition of platinum microcoils, and for the value of intra-arterial Amytal (amobarbital) testing to predict tolerance to embolization. In those cases in which focal neurological deficits developed with Amytal testing, embolization was not pursued. In procedures where silk or ethanol was also used, the analysis did not separate the additional materials. Only one of the AVM's reported here was not subsequently resected. Recognizing the limitations and bias inherent in the subjective evaluation of embolic materials, we attempted to rank the surgical characteristics of feeding vessels and AVM tissue itself with regard to ease of coagulation, retraction, and cutting of entering vessels embolized with unmodified IBCA (without the addition of acet ic acid or iophendylate), PVA with microcoils, and PVA alone. Since quantitative criteria do not exist, we ranked those materials on a scale of 1 (easiest) to 3 (most difficult). Our experience with silk and the combination of ethanol and microfibrillar collagen is limited, but they are similar to PVA in their surgical characteristics.

### Table 1

Embolic materials used in 108 patients treated for arteriovenous malformation*

<table>
<thead>
<tr>
<th>Embolic Material</th>
<th>Selective Cerebral Catheterization</th>
<th>Cervical Carotid Catheterization Only</th>
<th>Surgical Exposure of Feeders</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVA only</td>
<td>14</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>balloons</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PVA + balloons</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PVA + coils</td>
<td>35</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PVA, coils, silk, ethanol</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PVA, coils, silk</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PVA, coils, ethanol</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IBCA</td>
<td>0</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>spheres†</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>59</td>
<td>17</td>
<td>32</td>
</tr>
</tbody>
</table>

*Abbreviations: PVA = polyvinyl alcohol foam; balloons = detachable balloons; coils = platinum microcoils; silk = particles of surgical silk suture material, 5-0 silk cut to 1- to 2-cm lengths; ethanol = 33% ethanol mixed with microfibrillar collagen; IBCA = iobutyl cyanoacrylate.
† Patients embolized elsewhere with silicone spheres and referred to our center for surgery.

### Table 2

Surgical quality of embolic materials*

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ease of Cutting</th>
<th>Ease of Retraction</th>
<th>Ease of Coagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBCA</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>PVA</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PVA + coils</td>
<td>3†</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

* Evaluation based on a subjective scale from 1 (easiest) to 3 (most difficult). IBCA = iobutyl cyanoacrylate; PVA = polyvinyl alcohol foam; coils = platinum microcoils.
† Coils interfere with the ability to cut a vessel at the site of coil placement. If coils occupy the length of the vessel, the coil can be extremely difficult to cut.

**Material Characteristics**

We reviewed the literature relating to toxicity, metabolism or degradation, and mutagenesis or carcinogenesis of PVA and IBCA. Because NBCA is advocated as a substitute for IBCA,7 we sought toxicity and metabolism information relating to that compound also. These materials were judged as to their mutagenicity, toxicity, and to their recanalization potential or evidence of biodegradation. Scores were assigned as “0” (no evidence or unknown), “1” (suggestive evidence), and “2” (definite evidence). Pulmonary or venous embolization secondary to shunting through a malformation was not considered here, although it must be mentioned as a possible effect of the use of these compounds in an AVM.

**Results**

The results of our evaluation of surgical characteristics are summarized in Table 2. Overall, we believe that PVA in combination with microcoils allows the greatest ease of retraction and resection while still assuring occlusion of feeding vessels and embolization of the AVM nidus. Because of the difficulty in cutting the coils directly, we believe that the addition of PVA is advantageous as it allows a limited amount of coils to achieve final occlusion. Although ranked higher than PVA alone in retraction, ease of section, and ease of coagulation, the combination of PVA plus coils behaves similarly when coils are used to a limited degree. We have found the combination of PVA plus coils to result in significantly better angiographic results than the use of PVA alone.53

A tally of the presence or absence of complications related to the use of platinum microcoils and Amytal testing is presented in Table 3. No significant improvement in the complication rate was found due solely to the addition of coils (four complications in 25 cases without coils, compared to four complications in 57 cases with coils, p = 0.210, Mantel-Haensel test). However, the comparison of complications based on the use of Amytal testing is significant (seven complications in 31 cases without Amytal testing, p = 0.002, Mantel-Haensel test). These results have been reported, in part,
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### TABLE 3
Relationships between microcoil use, Amytal testing, and complications

<table>
<thead>
<tr>
<th>Coil Used</th>
<th>Amytal Testing</th>
<th>Complications</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>no</td>
<td>16</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>yes</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>no</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>yes</td>
<td>45</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 4
Assessment of mutagenicity, toxicity, and recanalization with three embolic materials

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mutagenicity</th>
<th>Toxicity</th>
<th>Recanalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBCA</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>NBCA</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PVA</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

* Evaluation score: 0 = no evidence or unknown; 1 = suggestive evidence; 2 = definite evidence. See text for discussion. IBCA = isobutyl cyanoacrylate; NBCA = n-butyl cyanoacrylate; PVA = polyvinyl alcohol.

elsewhere. Stratification of the Amytal test results based on the use or lack of use of platinum coils suggests a potential interaction between these two surgical practices. Without the use of coils, Amytal testing does not significantly alter the risk of complication (relative risk without Amytal testing = 0.98, p = 0.96, Mantel-Haensel test), but with the use of coils, the lack of Amytal testing carries a risk of complications approximately 31 times greater than with the use of Amytal testing (p < 0.001, Mantel-Haensel test, added to each cell to complete the relative risk estimate). A more rigorous test of interaction based on weighted least-squares or other categorical analysis techniques is deferred since no complications were seen when both platinum coils and Amytal testing were used.

Results of the review for mutagenesis, toxicity, and recanalization are summarized in Table 4. There are suggestions without definite proof of mutagenesis with PVA and acrylic glues. Polyvinyl alcohol is the least toxic of the compounds with regard to inflammatory reaction and angionecrosis. All compounds show some evidence of recanalization. Studies comparing them have not been performed, in part because of the lack of an adequate animal model for AVM’s.

### Discussion

**Subjectivity**

The authors recognize the subjective nature of some of the analysis presented above. In conducting that analysis, factors such as operative time, estimated blood loss at surgery, numbers of units of blood transfused, and neurological outcome were considered as possible areas of evaluation for better objectivity. However, this series was accumulated over more than a decade. During that time, anesthesia techniques and surgical approaches have evolved, in addition to the revolutionary changes in embolic approaches. To try to separate one or another of these factors became impossible, yet there were observations made in the operating room about different materials which we felt should be of interest to those involved in the treatment of this disease. It would have been less appropriate to try to impart objectivity in this situation than to try to open a discussion of surgical factors that have not been adequately discussed previously.

### Pharmacological Considerations

The utility of a compound or device for a given application can be seen in light of much the same considerations as a drug’s viewed: that is, for both its characteristics for achieving the desired effect and the risks inherent in its use. In the embolization of AVM’s, the desired effect relates to the surgical characteristics created by the embolic material. The risks relate to the permanence of the embolic effect, the toxicity of the compound, and the potential of the drug or device to incite mutagenesis. For this evaluation, we assume that the immediate risk of the embolization (stroke or hemorrhage) is similar for all materials and we assumed that the desired effect of initial vascular occlusion is achievable with any of these materials.

**Particle Variation.** Because PVA foam is not a standardized molecule, it can be polymerized to different molecular weights having different behaviors in the presence of some enzymes. For this analysis, only PVA foam sponge (as opposed to PVA base chemical or solutions) was considered. Caution should be exercised even in considering PVA foam. Although particles are sold as maintaining a certain size, variation from the purported size has been reported and has resulted in at least two infant deaths, probably due to pulmonary embolization.

**Tissue Response.** Assessment of the toxicity of compounds requires an evaluation of the specific tissue responses they elicit. For instance, IBCA has been shown to be associated with inflammatory responses in the surrounding vessels. Vinters, et al., also found widespread angionecrosis and sometimes extravascular bucculately associated with a dissolution of vessel walls. In a comparative study embolizing celiac and renal arteries in pigs, White, et al., found IBCA histologically presented as “a nonstaining, slightly refractile network surrounded by large numbers of foreign-body giant cells and organized thrombus. There were varying degrees of chronic inflammation, represented by lymphocytes and plasma cells in the thrombus and surrounding vascular tissues. The vascular outlines were retained, although the internal elastic lamella was often focally disrupted. In many cases, the arteries appeared

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to be dilated by their contents." In describing the histological appearance of PVA, they stated, "Giant cells were rare, and there was little inflammation in or around the area of thrombosis. The primary reaction was the formation of dense fibrous connective tissue in and around the sponge spicules." It appears that the tissue reaction to PVA is less intense than that to IBCA.

In that study, White, et al.,\(^4\) noted PVA to present histologically in only one of three animals embolized 3 to 5 months earlier with "varying amounts of Ivalon." Following injection of microemboli in rat carotid arteries, Quisling, et al.,\(^4\) identified PVA in the brain tissue of 34 of 35 animals sacrificed up to 9 months after injection. They also found no evidence of an inflammatory response in vessels embolized but not occluded.

**Particle Dissolution of PVA**

The possibility that PVA particles undergo dissolution following injection has not been discussed before but should be considered. Although widely mentioned, little has been written regarding recanalization with PVA.\(^3\) It is sometimes not clear whether the redevelopment of flow to an AVM following embolization with PVA is due to true recanalization or to the development of collateral flow, although some recanalization between particles clearly occurs when larger sizes are used. We do not challenge the possibility of recanalization, but our experience with many particle sizes over time has been that recanalization is limited or absent for at least a few weeks when occlusion is achieved with the smallest possible particles; however, new collaterals may develop more rapidly. We have also observed spasm fluoroscopically at the time of embolization in some cases; the subsequent relief of spasm could lead to apparent recanalization in a situation where true occlusion never existed. The adhesives, on the other hand, adhere to vessel walls and would not permit the vessel to dilate. We also believe the addition of microcoils to be very helpful in the prevention of recanalization and have shown improved results with them.\(^29\)

**Mutagenicity of PVA**

If PVA foam were shown to dissolve, the concurrent use of microcoils would help diminish reperfusion. In its base chemical form, PVA has been used for some time to produce an experimental glomerulopathy in animals.\(^2\)\(^-\)\(^7\)\(^-\)\(^40\) In one case report, repeated skin exposure to a PVA solution was reported in association with hemangiofibroma of the bladder.\(^11\) However, no reports of tumors of glomerulopathy in association with PVA foam embolization could be found. One group of researchers found that PVA was negative for mutagenicity\(^21\) using the Ames test, with which positivity has been demonstrated for NBCA.\(^28\)

Others have shown tumor development in animals with PVA.\(^29\) Dukes and Mitchley\(^12\) showed that tumor development was related to particle size, with their smallest implant being 2 cm × 2 cm × 2 mm thick. Interestingly, they demonstrated fragmentation of some of their sponge implants and subsequent migration of PVA fragments to surrounding tissues. We have not seen glomerulopathy or tumor development in any patients we have treated. Further studies of the long-term integrity of intravascular PVA sponge are warranted.

**Dissolution of IBCA.** There is strong evidence that IBCA may undergo long-term degradation. It is known that methyl, ethyl, and butyl esters of cyanoacrylate degrade in the presence of distilled water.\(^27\) In a study including 10 patients who had received IBCA embolization of their AVM's and subsequently undergone resection, Klara, et al.,\(^23\) found a "honeycombed lattice" within IBCA emboli containing intact red blood cells. If these had been trapped at the time of embolization, they should have dissolved and undergone fibrosis. No fibrotic changes were seen. Vinters, et al.,\(^45\) examined 17 AVM's resected 5 days to 16 months following embolization and observed that the estimated percentage of the cross-sectional channel area occupied by bucrylate was lower than the radiological estimate derived at the time of embolization in all but two cases. Lehman, et al.,\(^26\) applied various cyanoacrylate compounds to radial and peroneal nerves of dogs and followed them for varying times up to 36 weeks. They concluded that, "Less of each adhesive was present about those nerves which had been coated for longer periods of time."

In a separate study, Lehman, et al.,\(^26\) also found that various cyanoacrylates, including NBCA and IBCA, exhibit zones of inhibition when polymerized discs are placed in a bacterial culture medium inoculated with either Escherichia coli or Staphylococcus aureus. This was taken to indicate an inhibitory effect from a soluble breakdown product, either formalin or cyanoacetate.

Soluble degradation products have been implicated in cytotoxicity studies involving cultured mouse fibroblasts using NBCA.\(^13\) Rao, et al.,\(^35\) reported nine patients with large AVM's embolized with IBCA who had angiographically documented dissolution of IBCA with recurrence of their malformations at 6 to 20 months following embolization. Although cyanoacrylates are said to be biodegradable,\(^7\) the exact mechanism in vivo is poorly understood.

**Mutagenicity of IBCA.** There are also reports of unpublished animal studies showing carcinogenesis with methyl methacrylate\(^5\) and with IBCA,\(^30\) although reports of carcinogenesis in humans are lacking.\(^3\)

**Other Embolic Materials**

The authors realize that acrylic glues are used extensively in other centers and that modification of glues\(^6\) may result in surgical characteristics other than those described here. Comparative studies of the surgical characteristics of modified acrylics are sparse. Cromwell and Kerber\(^10\) found only a mild inflammatory response to a mixture of bucrylate and iophendylate, suggesting that tissue reactions may also be modified. However,
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This report is an attempt to review our experience with surgery on unmodified IBCA. Objective studies detailing in vitro criteria to quantify the surgical qualities we discuss could not be found, but would be worthwhile if appropriate models were used. We have included NBCA in the consideration of toxicity because of its being advocated as an embolic alternative to IBCA and to show that it also appears to share some of the tissue response qualities of IBCA. Less has been written about NBCA than IBCA in that regard. Brothers, et al.,1 studied NBCA extensively for its behavior as an embolic material and found it very similar to IBCA, including not only its flow and polymerization characteristics, but also its toxicity and recanalization potential. We find no descriptions of its surgical implications and we have no experience with NBCA in our series.

We found no long-term studies of the effects of the intravascular placement of platinum or of microcoil occlusion. Neither mutagenicity nor toxicity has been established. Barth, et al.,2 have shown chronic inflammatory reactions to steel coils with interwoven silk, wool, or Ivalon strands.

We have abandoned the use of detachable silicone balloons for AVM embolization due to the recent availability of platinum microcoils in combination with PVA and to the inability of balloons, when used alone, to reach the AVM nidus. Silicone spheres also do not reach the nidus of the AVM, and we do not employ them in our embolic practice.

Conclusions

Although it is possible to eliminate an AVM embolically by angiographic criteria, no published studies show a cure rate via embolization that is competitive with that of surgical resection. Therefore, there are four possible motives for embolic therapy: 1) palliation in a symptomatic patient with a nonresectable AVM or in whom resection carries unacceptable risk; 2) preoperative devascularization; 3) diminution of nidus size in combination with radiosurgery; and 4) as a therapeutic trial to see if surgery is avoidable in the minority of cases in which an angiographic cure is achieved. There are no studies suggesting that the incomplete embolic elimination of an AVM decreases the risk of subsequent hemorrhage or seizures.

We submit that palliation may be accomplished with any of the materials discussed here, as well as with surgical silk, microfibrillar collagen, alcohol, and other materials cited above and used by other authors. This is a separate topic and would require further investigation to resolve which material is preferable if such therapy is to be undertaken.

We further submit that of the materials with which we have experience, preoperative devascularization is best and most safely accomplished with a combination of PVA and microcoils. We have also found that the addition of limited amounts of 33% to 50% ethanol, with or without the addition of microfibrillar collagen, helps to incite thrombosis in situations where embolic material is in place and can serve as a nidus for that thrombosis. If some stasis is present, less ethanol compound is needed. If a therapeutic trial for avoiding surgery is to be advocated, materials must be developed that have been proven to lack recanalization or biodegradability potential.

The potential for recanalization with any material is irrelevant if surgical extirpation is performed prior to redevelopment of vascular channels.

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References


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