

# A mixture of ethylene vinyl alcohol copolymer and ethanol yielding a nonadhesive liquid embolic agent to treat cerebral arteriovenous malformations: initial clinical experience

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**Object.** The authors report their clinical experience with their new nonadhesive liquid embolic agent, an ethylene vinyl alcohol copolymer (EVAL)/ethanol mixture, to treat arteriovenous malformations (AVMs).

**Methods.** Between June 1995 and April 2001, 57 patients with confirmed AVMs underwent embolization of their lesions with the EVAL/ethanol mixture. In 87 procedures consisting of one to three stages, the authors embolized 185 feeding arteries to occlude as much of the AVM as possible. Repeated injections under fluoroscopic control could be performed smoothly without encountering cementing of the catheter to the vessel wall. Among the 87 embolizations undertaken in 57 patients, seven procedures (8%) in six patients produced new postembolization symptoms. Resolution of these symptoms occurred within hours or days after four of the seven procedures; permanent neurological deficits remained after the other three procedures (3.4%). Of the 57 patients, three underwent postembolization radiosurgery, and 54 underwent radical treatment with microsurgical extirpation. Histopathological examination of the 54 specimens disclosed mild inflammation within the embolized lumen without inflammatory reactions in the media or adventitia. Follow-up angiograms obtained 3 years after radiosurgery was administered showed that in all three patients treated in this fashion the nidus had completely disappeared.

**Conclusions.** The EVAL/ethanol mixture is handled easily and appears to be an effective and safe agent for preoperative embolization of AVMs.

**KEY WORDS** • arteriovenous malformation • embolic agent • embolization

**A**LTHOUGH nonadhesive liquid embolic agents may have advantages over currently available adhesive agents, they present a variety of real and potential disadvantages, most of which center on the use of DMSO as the solvent. Although the intravascular toxicity of DMSO could be controlled by slowing the injection rate in animal models, there remain safety concerns regarding its clinical use.<sup>2,15</sup> We developed a mixture of EVAL and iopamidol (Iopamiron; Nihon Schering, Osaka, Japan) dissolved in ethanol as an alternative solvent to offer a much safer means of embolizing AVMs.

In an experimental study<sup>10</sup> completed before this clinical investigation, we researched the properties, characteristics, and techniques of embolization related to our new EVAL/ethanol mixture. We found it to be easy to handle, safe, and effective in a rabbit model of renal artery em-

*Abbreviations used in this paper:* AVM = arteriovenous malformation; CT = computerized tomography; DMSO = dimethyl sulfoxide; EVAL = ethylene vinyl alcohol copolymer; ICA = internal carotid artery; MCA = middle cerebral artery; NBCA = *N*-butyl cyanoacrylate.

bolization. Particularly attractive were its nonadhesive character and the fact that it allowed for repeated injections. Therefore, we posited that as an adjunct to neurosurgery, embolization with the EVAL/ethanol mixture would provide reduced flow and occlusion to deep feeding arteries.

We now report on our initial clinical experience with EVAL/ethanol embolization. The study protocol was approved by the local ethics committee, and informed consent was obtained from all patients or their closest relatives before inception of the study.

## Clinical Material and Methods

### Patient Population

Between June 1995 and April 2001, 57 patients with confirmed AVMs underwent EVAL/ethanol embolization at Kumamoto University Hospital. Of these, 45 presented with hemorrhage from their AVM, six with at least one seizure episode, and two each with headache or visual field deficits; two patients were diagnosed incidentally.

These patients (32 males and 25 females) ranged in age from 8 to 63 years (mean age 32.7 years). According to the Spetzler–Martin grading system,<sup>25</sup> two lesions were Grade I, 16 were Grade II, 27 were Grade III, and 12 were Grade IV. Of the 57 lesions, 33 (57.9%) were located in the eloquent area of the brain. Using 87 one- to three-stage procedures, 185 feeding arteries were embolized to occlude as much of the AVM nidus as possible. Subsequent embolizations were performed after an interval of approximately 1 to 2 weeks. Postembolization, 54 patients were treated with radical microsurgical extirpation of their AVMs, and the other three refused resection, undergoing radiosurgical intervention instead.

#### *Embolization Procedures*

All procedures were performed in the interventional neuroangiography suite by using high-resolution digital subtraction angiography and the road-mapping technique. Embolization was performed via the transfemoral approach after application of local anesthesia; all patients were awake throughout the procedure, with the exception of five children younger than 12 years in whom we induced general anesthesia. A No. 6 French sheath was placed into the femoral artery and a No. 6 French guiding catheter was inserted through the sheath. Systemic anticoagulation was achieved during the procedures with a 3000-U bolus of heparin, followed by 1000 U of heparin every hour. Most embolizations were performed with a Tracker-18 catheter (Target Therapeutics, Fremont, CA). The tip of the microcatheter was gently guided into the proper artery and carefully positioned as close as possible to the AVM nidus. After superselective angiography, an appropriate dose (usually 30–50 mg) of amobarbital (amytal sodium; Eli Lilly and Co., Indianapolis, IN) was injected to evaluate the patient for potential neurological deficits, and immediate examination was performed to detect deficits related to this injection. In the five children in whom general anesthesia had been induced, the provocative testing was not performed. After confirming a negative amobarbital test, 0.6 ml of 30% ethanol (slightly in excess of the amount needed to fill the 0.53-ml Tracker-18 catheter) was injected to irrigate the catheter lumen. This was followed by injection of the EVAL/ethanol mixture with a tuberculin syringe, which we repeated until complete obliteration of the AVM was confirmed under direct fluoroscopic viewing. Because the material is not adhesive and has a low viscosity, multiple injections could be administered.

To assess the progress of the embolization, we performed angiographic studies by using the guiding catheter during a pause in the injection. At the end of the procedure, the catheter was withdrawn slowly and a final angiogram was obtained to check the occlusion of the embolized artery. Depending on the size of the AVM, one or two more injections were made into different feeding vessels. If the material was observed to pass through the nidus and into the draining vein, the injection was halted for 2 or 3 seconds and then resumed. This procedure was continued until the proximal reflux of the material began to extend along the microcatheter or until the nidus was filled and there was no more deposition of the material. All catheters used during the procedure, including the guiding catheters and the microcatheters, were continu-

ously flushed with heparinized saline (5000 U/L) by using an infusion pump.

To treat high-flow lesions, we performed vascular inflow occlusion by using an occlusion balloon catheter to slow the shunt movement through the AVMs. The balloon catheter was placed in the cervical ICA, and vital signs and neurological function were monitored during and after the procedure. The patients were subsequently moved to the intensive care unit for further observation. On the 1st postoperative day, all patients underwent CT scanning for evaluation of edema, mass effect, infarction, or hemorrhage. In patients undergoing more than one embolization procedure, each postembolization CT scan was compared with the most recent previous one. After 1 to 2 days in the intensive care unit, the patients were moved to the neurosurgical ward until discharge. Their clinical outcomes were evaluated by chart review.

The postembolization course was defined as asymptomatic or symptomatic. Symptomatic patients were defined as those exhibiting either generalized or focal neurological deficits. Progressively improving postembolization changes in neurological status that resulted in a complete return to the baseline preembolization status were considered transient. Neurological deficits that did not improve or that failed to return to the preembolization baseline were considered permanent. Patients in whom neurological deficits were observed during or after embolization underwent further evaluation.

The interval between the last embolization and surgery was approximately 1 to 2 weeks. Surgical specimens, fixed in 10% neutral buffered formalin and routinely processed for light microscopy, were sectioned at 3  $\mu$ m and stained with both hematoxylin and eosin and elastic van Gieson.

#### **Results**

A total of 87 procedures were performed; 32 patients underwent one procedure, 20 patients required two, and five required three serial procedures. Typical injection volumes were between 0.7 and 0.9 ml and the mean injection time was 2 to 3 minutes. Mean volumes and injection times increased as we acquired more experience with the procedure. The embolization material had a low viscosity and easily passed through the narrow lumen of the microcatheter, even the Tracker-10 catheter. Repeated injections under fluoroscopic control went smoothly; we encountered no cementing of the catheter to the vessel in any of the procedures. Complete vessel occlusion was confirmed angiographically immediately after the embolization procedure (Fig. 1). No patient experienced ethanol toxicity. We did not encounter occlusion of any of the draining vessels during the embolization procedure; however, in four large feeding vessels we noted partial occlusion of the draining venous outlet. None of our patients experienced peri- or postembolization intracranial hemorrhage from normal pressure breakthrough or venous outlet obstruction.

In six patients undergoing a total of seven embolization procedures (8%) we noted new clinical symptoms after embolization; CT scans demonstrated ischemic changes that correlated with these symptoms. They were motor weakness (four patients), new visual field deficits (two patients), and comprehension or memory disturbance (two

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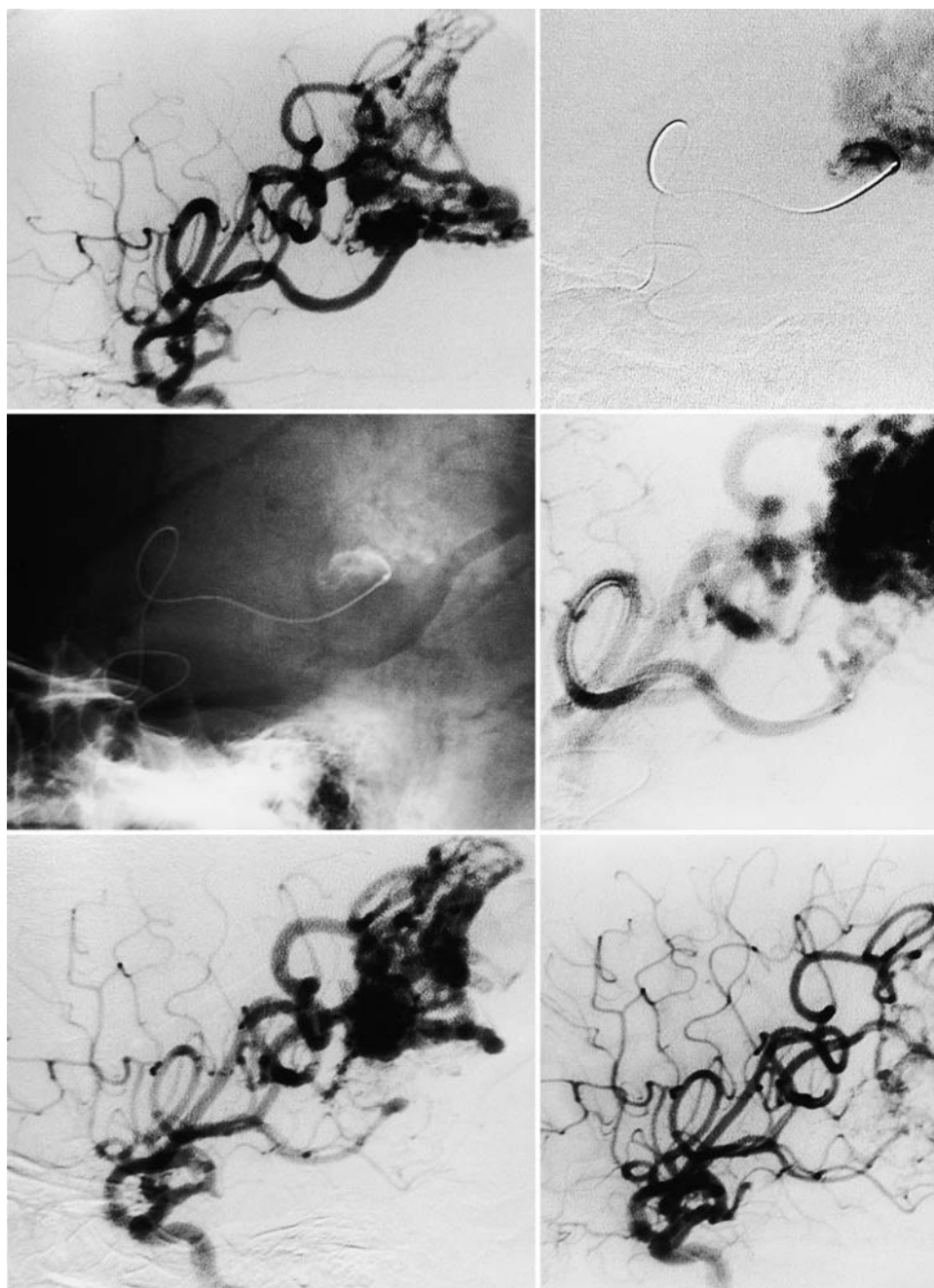


FIG. 1. Illustrative case of a patient who underwent embolization followed by surgery for an AVM. This 23-year-old man with a history of medically controlled seizures presented with severe headache. Admission CT scan revealed an intracerebral hemorrhage in the left parietal lobe. Feeding vessels were derived from the MCA; venous drainage was superficial. *Upper Left:* Lateral view, angiographic study of the left ICA demonstrating these findings. The patient underwent a two-stage embolization. A large branch arising from the inferior trunk of the MCA and leading to the AVM was catheterized first. *Upper Right:* Superselective angiogram providing a lateral view of the tip of the microcatheter and the filled part of the nidus. *Center Left:* The EVAL/ethanol mixture was injected through the microcatheter under direct fluoroscopic view. *Center Right:* Further EVAL/ethanol infusion, without removal of the microcatheter, to evaluate nidus obliteration and additional delivery of the mixture through the same microcatheter. *Lower Left:* The feeding artery arising from the inferior trunk of the MCA is seen to be completely embolized. Eventually, a total of four separate feeding vessels were embolized. *Lower Right:* At the conclusion of the embolization procedures, there is a significant reduction in blood flow through the nidus. Resection was performed 1 month after the first embolization, and the postoperative angiogram demonstrates complete resection of the AVM.

patients); two of the six patients presented with two symptoms. In four of these seven procedures, symptom resolution occurred within hours or a few days after onset. Of the 87 procedures, three (3.4%) resulted in new permanent

neurological deficits. Postembolization CT scans revealed new abnormalities after three embolization procedures performed in three patients; however, all of these patients remained asymptomatic.

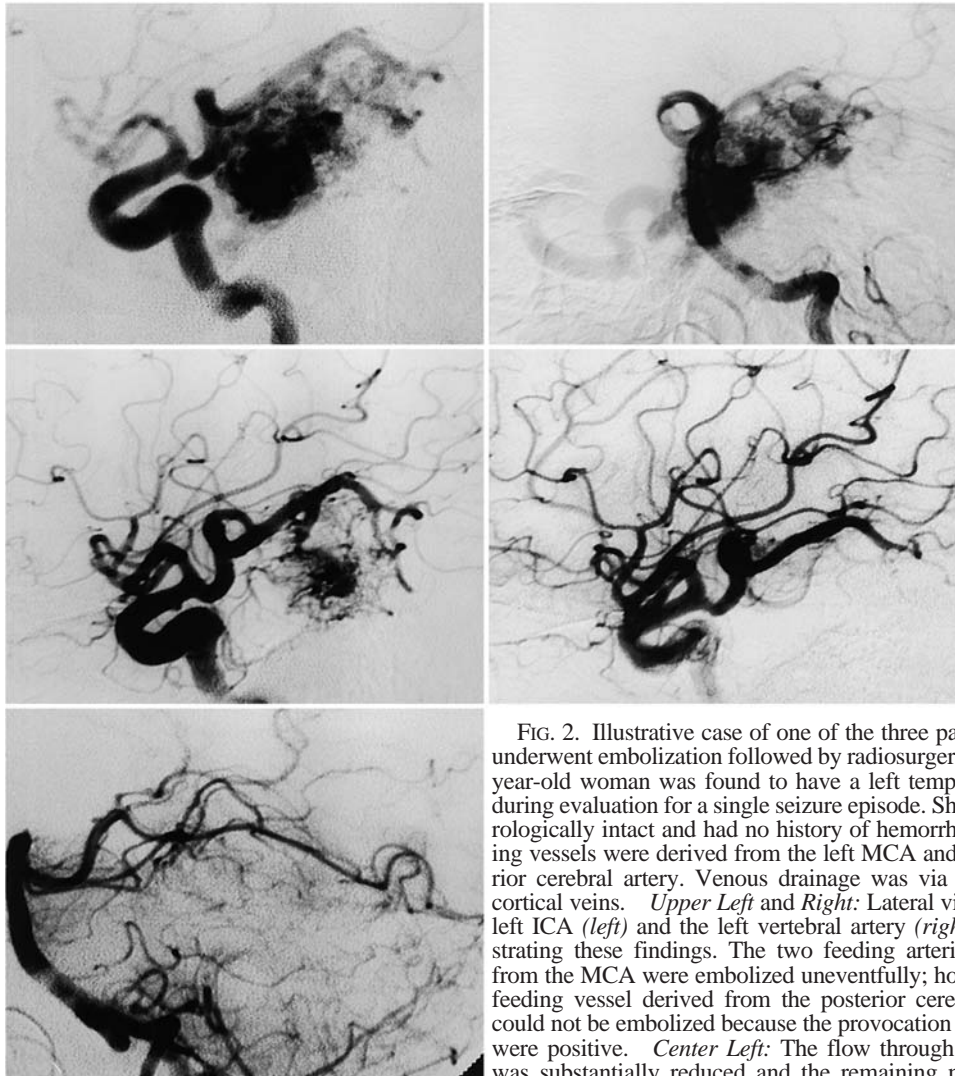


FIG. 2. Illustrative case of one of the three patients who underwent embolization followed by radiosurgery. This 32-year-old woman was found to have a left temporal AVM during evaluation for a single seizure episode. She was neurologically intact and had no history of hemorrhage. Feeding vessels were derived from the left MCA and the posterior cerebral artery. Venous drainage was via superficial cortical veins. *Upper Left and Right:* Lateral views of the left ICA (*left*) and the left vertebral artery (*right*) demonstrating these findings. The two feeding arteries derived from the MCA were embolized uneventfully; however, the feeding vessel derived from the posterior cerebral artery could not be embolized because the provocation test results were positive. *Center Left:* The flow through the AVM was substantially reduced and the remaining nidus measured less than 25 mm. The patient underwent radiosurgery 2 weeks after the embolization. *Center Right and Lower Left:* Follow-up angiograms obtained 38 months later showing complete disappearance of the AVM. The patient remained asymptomatic throughout the treatment period.

Of the 57 patients, all but three who declined surgical treatment, underwent excision of their AVM; the other three patients were treated with radiosurgery. At surgery, the color of the embolized feeding vessel and the nidus was observed to have changed to white, partially mixed with dark brown. The AVMs were soft enough to allow retraction from surrounding normal tissues; coagulation and sectioning with microscissors were easily achieved. In the three patients who underwent embolization followed by radiosurgery, the AVM measured approximately 40 mm on the initial angiograms. After embolization, the residual nidus was less than 25 mm, and at the 3-year follow-up review, angiograms confirmed its complete disappearance (Fig. 2). Only long-term follow up will determine the degree of permanence of this treatment.

All 54 surgical specimens were histopathologically analyzed. The light gray EVAL sponges were found to be in direct contact with the entire circumference of the endothelial surface, and old hemolyzed red blood cells were entrapped within the sponges. In patients who underwent

excision within 2 weeks of embolization we noted varying degrees of inflammation, manifested by the presence of a few lymphocytes and neutrophilic granulocytes within the embolized lumina. Although there was complete endothelial denuding and intimal damage, the internal elastic lamina was only focally disrupted; there were scarcely any inflammatory infiltrates in the media and adventitia (Fig. 3). In patients who underwent excision more than 2 weeks after embolization, these histopathological changes were slightly more pronounced; however, there was no evidence of intramural hemorrhage or extravasation of the embolization material (Fig. 4).

### Discussion

Luessenhop and Spence<sup>14</sup> first introduced the embolization of cerebral AVMs in 1960, and the transfemoral approach has been used to embolize brain AVMs. Since then, embolization of vascular lesions in the brain has developed as an important specialty in neurosurgery. Col-

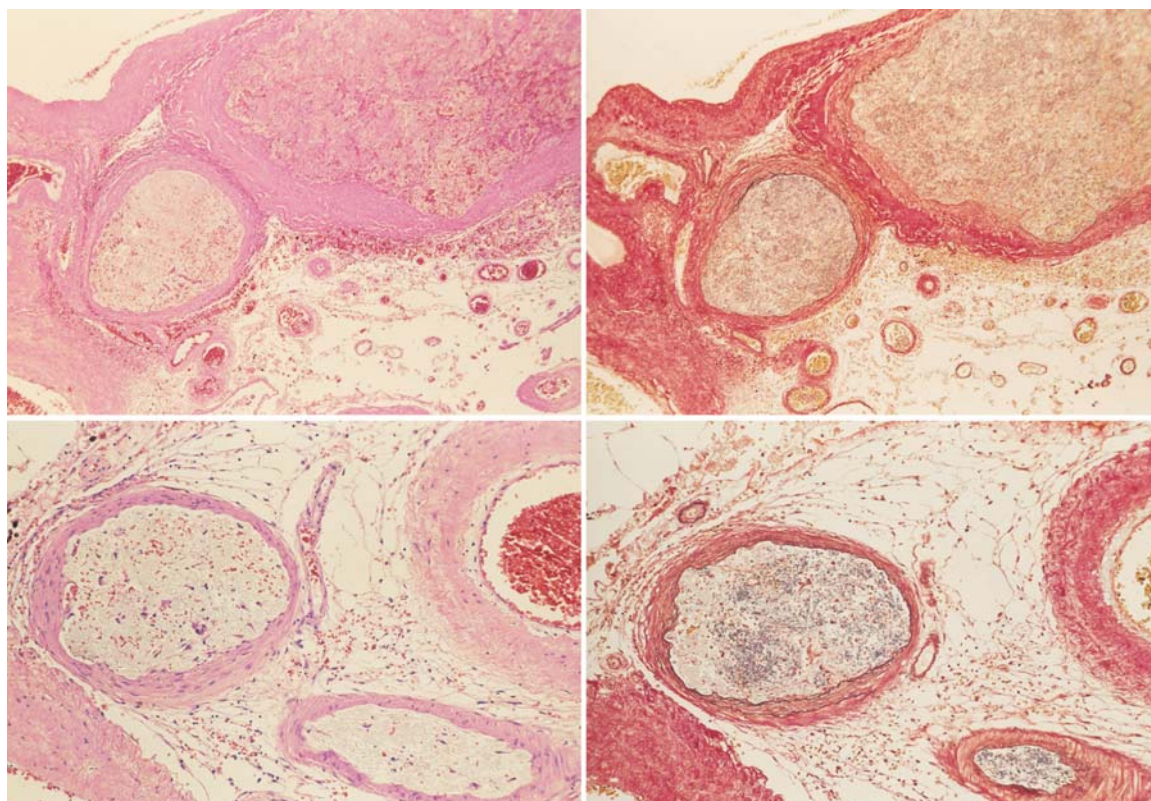


FIG. 3. Photomicrographs showing two surgical specimens that were excised within 2 weeks after embolization of AVMs. The light gray EVAL sponge is in direct contact with the entire circumference of the endothelial surface. A few inflammatory cells are seen among old, hemolyzed red blood cells within the embolized lumina. The internal elastic lamina is focally disrupted and there are hardly any inflammatory infiltrates in the media and adventitia. H & E, original magnification  $\times 10$  (upper left); elastica van Gieson, original magnification  $\times 10$  (upper right); H & E, original magnification  $\times 20$  (lower left); elastica van Gieson, original magnification  $\times 20$  (lower right).

laborative efforts among neurosurgeons, neurologists, and interventional neuroradiologists have spread the use of cerebral endovascular procedures as a preoperative adjunct, and in select cases they are now a primary mode of therapy in many types of vascular lesions.<sup>9,12,13,16,18-20,23</sup> Since the 1980s, microcatheters have been devised that can be used to gain access to the most distal cerebral circulation. Concurrently, many embolic agents have been developed that are now routinely used to perform embolization procedures by using these microcatheters.

Nevertheless, the ideal material for embolization of AVMs has yet to be discovered, and it is important for the success of interventional neuroradiology that different types of embolization materials continue to be developed and evaluated. The optimal embolic agent is not biodegradable, and it is nontoxic and nonmutagenic.<sup>19</sup> It should be easily delivered through a microcatheter, easily seen on fluoroscopy, and it should adhere to the vessel wall without extravasation or recanalization. Finally, the ideal embolic material should be soft enough to allow retraction of the lesion from surrounding normal tissues during surgery.

#### *Comparison of the EVAL/Ethanol Mixture With Other Embolic Agents*

Many embolic agents have been used in the treatment of brain AVMs. The most widely used embolic materials consist of varying sizes of polyvinyl alcohol derivative, microcoils, silk sutures, absolute ethyl alcohol, and vari-

ous tissue adhesives.<sup>5,18,20,22,24,29</sup> Polyvinyl alcohol does not provide permanent occlusion, and the choice of particles that are too small may result in fatal pulmonary insufficiency, because the particles are radiolucent. Coils produce very proximal occlusion, they do not occlude at the nidus, and they are not easily resectable. Although silk sutures are inexpensive and readily available, they can induce an intense inflammatory response, they are difficult to see, and their ultimate location is frequently unknown. Ethanol is also inexpensive and easy to deliver, and although it appears to be very effective in occluding the blood vessel, safety concerns limit its use.

Among liquid embolic agents, NBCA (Cordis Neurovascular Inc., Miami, FL) is now the most extensively used. The intranidal infusion of NBCA is successful in some cerebral AVMs, and it has recently received approval from the United States Food and Drug Administration for the treatment of cerebral AVMs. Nevertheless, there are some risks and complications that are relatively specific to embolization with cyanoacrylate adhesives. Cyanoacrylate is almost immediately polymerized on contact with the vascular endothelium and ionic fluids such as blood. Therefore, modification of the polymerization process is required to allow for safe delivery of NBCA through a microcatheter.<sup>1</sup> If the polymerization time is too long, the material will migrate through the nidus and be polymerized within the venous drainage of the AVM, resulting in venous occlusion and consequent venous infarct-

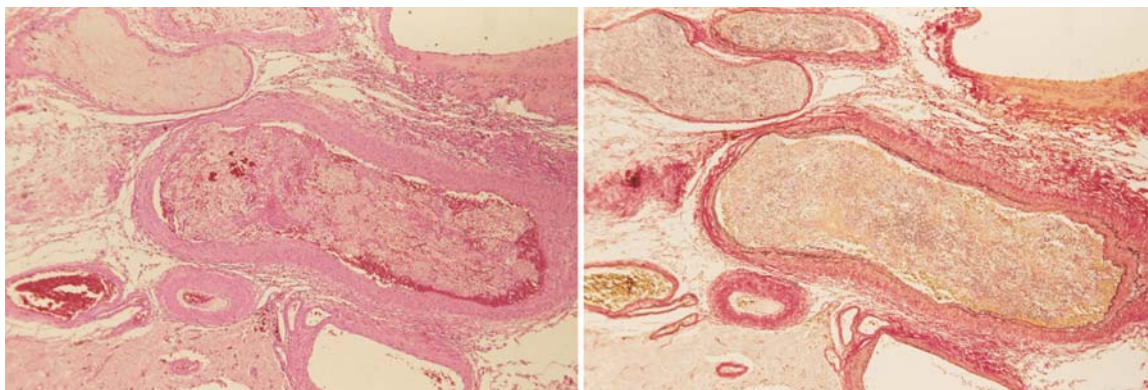


FIG. 4. Photomicrograph showing a surgical specimen that was excised more than 2 weeks (20 days) after embolization. Intensification of the inflammatory changes is seen within the embolized lumina and vessel wall. The vascular outlines are completely retained, however, and there is no evidence of intramural hemorrhage or EVAL extravasation. H & E, original magnification (*left*); elastica van Gieson, original magnification  $\times 10$  (*right*).

tion or intranidal hemorrhage. If polymerization occurs too rapidly, the arterial feeding pedicle will be occluded before the nidus, allowing nidus revascularization and the development of a collateral supply. Suh, et al.,<sup>26</sup> reported that the degree of premature polymerization was different for different lots of Lipiodol and different NBCA concentrations. Therefore, significant precautions must be taken to achieve appropriate polymerization times. Although NBCA is an excellent embolization agent in cases in which the microcatheter can be placed inside the nidus, the positioning of the microcatheter in the nidus can be difficult, prolonging the procedure time and increasing the risk of stroke. Embolization with tissue adhesives entails the risk of permanently gluing the catheter tip within the cerebral vessel; therefore, the successful use of this agent is critically dependent on the skill and experience of the operator. Furthermore, excision after the use of tissue adhesives can be complicated; although these agents are now highly diluted with Ethiodol, surgical retraction, cutting, and coagulation can be somewhat difficult.

In 1990 Taki, et al.,<sup>27</sup> developed the original formulation of Onyx (Onyx Liquid Embolic System; Micro Therapeutics, Inc., Irvine, CA). It was used extensively in Japan to treat cerebral AVMs and for tumor embolization. More recently, Onyx has been used in Europe, and it is currently being investigated as an embolic material in the United States for treatment of both cerebral AVMs and large and giant intracranial aneurysms.<sup>11,28</sup> Onyx is a liquid, opaque embolic material that is easily injected through a microcatheter; its nonadhesive nature allows for a more controlled and longer delivery process without the catheter becoming glued to the vessel wall. In addition, this material is supplied in premixed vials, and no preparation is required before injection.

The use of DMSO as the solvent for Onyx, however, is a distinct disadvantage. If it is given at too high a volume or concentration, DMSO is toxic to blood vessels and may lead to acute vessel damage, necrosis, or vasospasm; therefore, only small amounts of DMSO can be injected directly into cerebral blood vessels over certain time periods. Thus, the therapeutic window is at best relatively narrow and safety concerns regarding the use of DMSO remain. In addition, the use of DMSO as a solvent requires an appropriate, compatible delivery system because DMSO

dissolves the plastics used in the manufacture of many kinds of commercially available microcatheters.

Mindful of the attractive properties of EVAL, we developed an EVAL/ethanol mixture that uses ethanol as the alternative solvent. In the clinical setting, we found that it handled easily, and its delivery through the microcatheter could be achieved smoothly because of its low viscosity. Because the mixture is completely nonadhesive, multiple injections can be performed using the same microcatheter without the danger of it becoming cemented into place; microcatheter withdrawal after embolization was smooth in all 87 procedures. In high-flow AVMs, the EVAL/ethanol mixture was less than optimally radiopaque at the beginning of embolization; however, the degree of nidus occlusion and the status of the draining veins could be checked by repeated angiograms. The possibility of obtaining angiograms during the injection of the medium provided a considerable advantage because it allowed us to monitor the degree of the nidus obliteration and to check the state of the pertinent draining veins. Furthermore, the mixture was easily identified fluoroscopically during slowing of the vascular flow.

#### *Permanence of the Material*

Permanence is an important issue with embolic agents used to occlude AVMs, particularly when embolization is performed in conjunction with radiosurgery. Yakes, et al.,<sup>29</sup> reported a series of 17 AVMs that they embolized with absolute ethanol. They achieved angiographically confirmed cure in 41% of their patients; the mean follow-up period was 13 months. Although recanalization of the nidus after embolization with ethanol appears to be rare, embolization with NBCA, resulting in dense casting of the nidus, is thought to have a higher angiographically confirmed cure rate than embolization with other available agents. Our experimental study<sup>10</sup> was not designed to assess the permanence of EVAL/ethanol embolization; the rabbit kidneys were evaluated pathologically 4 months after embolization. We are not aware of any reports that EVAL is carcinogenic in humans, and the mutagenicity of this material is unknown. For these reasons, we used the mixture only as a preoperative adjunct. Angiographic studies obtained in all three patients who underwent radio-

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surgery because they refused excision of their AVMs demonstrated cure; the mean follow-up period in this group was 35 months. Nevertheless, larger patient populations and longer follow-up periods must be evaluated before it is possible to draw any conclusions regarding the degree of permanence of our EVAL/ethanol mixture.

### Postembolization Complications

The most common significant complications resulting from embolization were cerebral infarcts identified on CT scans. Of 87 procedures, seven (8%) resulted in new clinical symptoms, three (3.4%) in permanent neurological deficits, and four (4.6%) produced transient symptoms that resolved over the course of hours or within a few days after embolization. In all patients with permanent neurological deficits or transient symptoms, new areas of hypodensity caused by inadvertent occlusion of normal arteries were observed on CT scans; these correlated with the symptoms. In other series endovascular complication rates of between 3 and 25% have been reported.<sup>3,4,6,7,17,21</sup> The complications we encountered were no different in nature or frequency from those that are generally found after cerebral embolization, regardless of the embolic material used.

We encountered no occlusion of draining venous outlets during embolization; however, partial venous outlet obstructions were produced in four large feeding vessels. Because this complication appears to be relatively specific to embolization with our mixture, this material may not be suited for use in some lesions such as single arteriovenous fistulas or AVMs that contain a large arteriovenous fistula. For application in these cases, a mixture with more easily controllable polymerizing time is necessary.

The benefits of AVM embolization must be weighed against the risk of producing serious complications. Continued improvements in embolization procedures and devices will surely enhance the therapeutic success rate and decrease the complication rate. For the optimally safe and effective treatment of specific vascular lesions, the first step consists of clearly identifying the lesion by using neuroimaging or physical examination and of defining the goal of embolization. When embolization is used as an adjunct to surgery, its goal is to enhance the safety of surgery, usually by reducing the blood flow to the AVM and by occluding deep feeding arteries, which can be difficult to control at the time of excision.

### Histopathological Findings in the Surgical Specimens

Histopathologically, most of the surgical specimens were similar to the subacute specimens described in our experimental study.<sup>10</sup> Our findings differed from those of Fukushima, et al.,<sup>8</sup> who reported that after 4 weeks, cerebral AVMs embolized with an EVAL/DMSO mixture exhibited extensive endoluminal and intramural inflammatory infiltrates and perivascular hemorrhage. Considering the elapsed time between embolization and excision, our surgical specimens showed less inflammatory reaction in the vessel wall than did specimens embolized with an EVAL/DMSO mixture. Jahan, et al.,<sup>11</sup> used Onyx to treat 23 patients with cerebral AVMs; in two of 11 patients who had undergone resection 1 day after embolization, histopathological examination of the resected AVM revealed

angionecrosis involving many vessels. From this we infer that exposure of the microvasculature to DMSO may play a major role in the histopathological response to this material. Our experimental study<sup>10</sup> revealed that EVAL was not extravasated and that there was no intramural hemorrhage in the renal vessels embolized with the EVAL/ethanol mixture. At present we cannot explain this difference between our embolization materials and others; however, our findings support our contention that the EVAL/ethanol mixture may be a highly desirable embolic agent for the preoperative embolization of cerebral AVMs.

### Conclusions

The EVAL/ethanol mixture was easy to handle and appears to be an effective and safe embolic agent for the preoperative embolization of cerebral AVMs. Our preliminary study points to the feasibility of using this agent in the clinical setting. Nevertheless, because its safety and superiority over currently available embolic agents can only be demonstrated after further long-term studies, its use should be limited to patients already scheduled for excision of their AVMs.

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