Endovascular Treatment of Brain Arteriovenous Malformations Using Onyx: Preliminary Results of a Prospective Multicenter Study

L. PIEROT, A. C. JANUEL*, D. HERBRETEAU**, X. BARREAU***, J. DROUINEAU****, J. BERGE***, N. SOUROUR*****, C. COGNARD*

Department of Radiology, Hôpital Maison-Blanche; Reims, France

** Department of Neuroradiology, Hôpital Purpan; Toulouse, France*

*** Department of Neuroradiology, Hôpital Bretonneau; Tours, France*

**** Department of Neuroradiology; CHU Bordeaux, France*

***** Department of Radiology; Poitiers, France*

****** Department of Neuroradiology, Hôpital Pitié Salpêtrière; Paris, France*

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Summary

The main final goal of the treatment of brain AVMs is to prevent bleeding and to obtain a complete occlusion of the nidus. The strategy of treatment of brain arteriovenous malformations (AVM) has to be defined by a multidisciplinary team and will usually combine several modalities (surgery, radiosurgery, embolization). Embolization is generally the first step of treatment. Occasionally embolization is able to completely occlude a small AVM.

Otherwise embolization is the first step before surgery or radiosurgery. Several embolic agents have been proposed for embolization of brain AVMs like particles or cyanoacrylates. The main disadvantage of particles is the high frequency of recanalization.

The cyanoacrylates are probably more appropriate, providing a permanent occlusion. However, due to the polymerizing characteristics of the glue, the time of injection is relatively short (few seconds or minutes) and a complete or substantial occlusion of the nidus is difficult to obtain, especially in the case of medium or large-sized AVMs.

Onyx is a nonadhesive liquid polymer made

of a mixture of ethylene-vinyl-alcohol copolymer and dimethylsulfoxide. The theoretical advantage of a nonadhesive liquid is to eliminate the risk of gluing the microcatheter and subsequently to perform a more durable injection with a larger amounts of agent delivered in a single injection.

Several French centers have undertaken a prospective, multicentric study to evaluate the clinical value of Onyx in embolization of brain AVMs. As required, 50 patients were included. Preliminary results are presented regarding the first 48 patients, the last 2 patients being included after writing of this paper.

The treatment is now completed in 15 patients. As expected, it was possible with Onyx to perform long duration injections (5 to 70 minutes with a mean of 34 minutes).

Volumes injected per session were also important (0.25 to 6 ml with a mean of 1.6 ml). According to the clinical experience of the centers, duration and volume injected were most important with Onyx than with cyanoacrylates. Out of the 15 patients for whom embolization is now completed, 14 had a percentage of occlusion of the nidus greater than 60% (with 2 complete occlusion).

With regard to procedural complications, four acute postembolization hemorrhages (APEH) were observed (8% per patient, 4% per procedure). This rate of APEH is in the same range as with cyanoacrylates.

Introduction

The indications for treatment, goal of treatment and therapeutic strategy for brain arteriovenous malformations (bAVMs) are always a matter of debate and should be defined on a case-by-case basis by an experienced multidisciplinary team including neurosurgeons, radiotherapists and neuroradiologists¹. Indications for treatment basically depend on clinical presentation, patient characteristics including age, and anatomic features.

The goal of treating bAVMs is to eliminate the risk of hemorrhage and then to completely eliminate the AVM. For this purpose, several therapeutic approaches are available including neurosurgery, radiosurgery and embolization.

Embolization is often considered the first step of the therapeutic strategy. Its goal is to occlude the AVM or to decrease its size in order to make surgery or radiosurgery feasible. Embolization of bAVMs has developed in the last 35 years and the technique has evolved tremendously as a result of improvement of imaging techniques, advances in catheter and guidewire technologies and development of various therapeutic agents including silastic spheres, PVA and cyanoacrylates (nBCA).

Particulate embolization has some limitations (frequent recanalization of the nidus, risk of migration of particles in normal adjacent branches, and risk of the particles reaching the venous side of the AVM). Particles are almost no more used and only for preoperative embolization.

Intranidal embolization with cyanoacrylates has been considered for some time the most appropriate technique to obtain a stable occlusion of the nidus. However there are some limitations in the use of cyanoacrylates. NBCA is difficult to control due to rapid polymerisation and the corresponding very short time of injection (few seconds or minutes). Other limitations of nBCA are the low volume of any single injection, the need of rapid catheter withdrawal and the risk of catheter sticking. For these reasons treatment of large AVMs and complete occlusion of AVMs with nBCA is very difficult.

Onyx is a radiopaque, non-adhesive embolic fluid which precipitates upon contact with blood. Its use was proposed in 1996 for the embolization of brain AVMs and monocentric series have reported interesting preliminary results²⁻³.

The goal of our work is to evaluate precisely the clinical use of Onyx in the embolization of brain AVMs, in terms of safety and efficacy. The intent of our study was to include 50 patients with brain AVMs treated with Onyx and the 50th patient was included in March 2005. At the time of writing 48 patients were included and a first analysis regarding safety and efficacy is presented.

Material and Methods

A prospective, multicentric study was undertaken in eight french neurointerventional centers (Toulouse, Reims, Bordeaux, Clermont-Ferrand, Tours, Angers, Poitiers, Paris). The protocol was approved by the Ethics Committee of Reims. Informed consent was obtained from all patients.

According to the intent of the study, 50 patients were included from May 2003 to March 2005. At the time of writing, 48 patients were included (25 females and 23 males) and analysis was conducted in this group.

Patient age was between 16 and 64 years with a mean of 41 years. Clinical presentation was hemorrhage in 21 cases (44%), seizures in 16 cases (33%) and others in 11 cases (23%).

AVMs were located in the hemispheres in 41 cases, in the corpus callosum in 4 cases, in the basal ganglia and thalamus in 2 cases and in the cerebellum in 1 case.

Size of the AVM was:

- < 3 cm in 12 cases (25%)
- 3 to 6 cm in 31 cases (65%)
- > 6 cm in 5 cases (10%)

Venous drainage was deep in 9 cases (19%), superficial in 27 cases (56%) and deep and superficial in 12 cases (25%). Venous drainage was unique in 9 cases and multiple in 39 cases (81%).

Procedures were performed with the patients under general anesthesia. Steps of the procedures were superselective catheterization of the nidus using a DMSO compatible microcatheter and microguidewire (Ultraflow and Mirage, Micro Therapeutics, Inc.). The microcatheter tip was placed as close as possible to the AVM

nidus. Before injection of Onyx, the microcatheter was flushed with normal saline and the catheter dead space was filled with 0.25 ml DMSO. Then 0.25 ml Onyx was slowly injected (60 seconds) to fill the microcatheter and replace the DMSO in the catheter dead space. Slow injection of the Onyx was then continued under fluoroscopy. In case of reflux, the injection is stopped for 2 minutes. In case of venous passage, injection is briefly stopped. Various techniques were used to withdraw the microcatheter (slow continuous traction, fast traction).

Results

Technical Results

103 sessions of embolization were performed: 1 to 8 sessions / patient with a mean of 2 sessions. Duration of injection was 5 to 70 minutes with a mean of 34 minutes.

The volume injected per session was 0.25 to 6 ml with a mean of 1.6 ml.

Technical Problems

Perforation or dissection of the feeding pedicle without bleeding was observed in 4 cases. Withdrawal of the microcatheter was impossible in 2 cases. Rupture of the microcatheter was reported in 1 case and cervical dissection in 1 case (created by the guiding catheter).

Clinical Complications

Acute post-embolization hemorrhage was observed in 4 cases (8% per patient, 4% per session). In all cases, APEH occurred in the hours following embolization. Hematomas were surgically treated in all but one case. Surgical evacuation of the hematoma was not performed in one case, because a large portion of the nidus was not embolized and the neurosurgeon was cautious regarding the possibility of having a good control of the operative bleeding. This untreated patient eventually died. In the 3 other cases, a neurological deficit was observed in the months following the bleeding.

The size of the ruptured AVM was less than 3 cm in one case, 3 to 6 cm in two cases and more than 6 cm in one case. The volume of Onyx injected during the session before hemorrhage was 0.6, 1.5, 4.2 and 5.5 ml. The duration of injections were, respectively, 30, 52, 70

and 35 minutes. Techniques used to withdraw the microcatheter were various.

Non hemorrhagic deficits were encountered in 4 cases: cerebral ischemia in 3 cases and spinal cord ischemia in 1 case. Deficit was transient in 2 cases and permanent in 2 cases.

Anatomical Results

Endovascular treatment is now completed in 15 cases.

Percentage of occlusion is 100% in 2 cases, 80 to 99% in 9 cases, 60 to 79% in 3 cases and less than 60% in 1 case.

Discussion

The primary goal of the treatment of brain AVMs is to prevent bleeding and for this purpose complete exclusion of the AVM is necessary. Various techniques are available to treat brain AVMs (surgery, radiosurgery and embolization) and an association of techniques is often necessary to obtain a complete treatment of the AVM. Embolization is often the first step of the treatment to try to obtain a complete occlusion of the nidus or to prepare a subsequent treatment (surgery or radiosurgery). Various embolic agents have been proposed for the treatment of brain AVMs (particles, cyanoacrylates). The Onyx Liquid Embolic System (Micro Therapeutics, Inc.) is a new, non adhesive agent. Onyx is made of a mixture of ethylene-vinyl alcohol copolymer (EVOH) and dimethyl sulfoxide (DMSO). The EVOH is dissolved in the DMSO at various concentrations: 6%, 6.5% and 8%. Animal studies have shown that Onyx is capable of producing permanent occlusion of swine rete mirabile with the development of mild intra- and perivascular inflammatory changes and no clinical complications⁶. A fast injection of DMSO causes endothelial necrosis and severe inflammatory response in the arterial wall but the slow endovascular delivery produces no angiographic, pathological, or clinical changes. These results were confirmed by Chaloupka et al in 1999⁷ and subsequently the method of using Onyx in brain AVMs was defined. A first series reporting a single center clinicopathological experience with Onyx was published in 2001². Twenty-three patients were treated and 129 arterial feeders were embolized. Average AVM volume reduction after embolization was 63%. Single injections were

carried out for up to 12 minutes. Volume of Onyx injected were not reported. Four adverse events were observed. Two patients experienced ischemia because of inadvertent occlusion of an arterial feeder. One of these patients had a permanent deficit. Two other patients experienced transient neurological deficits that resolved within 1 week after embolization. There were no hemorrhagic complications. Permanent morbidity was thus 4%. There were no deaths. The results of our series are different. The duration of injection was 5 to 70 minutes with a mean of 34 minutes and volumes of Onyx injected were 0.25 to 6 ml with a mean of 1.6 ml. Due to the fact that Onyx is a nonadhesive polymer, the risk of gluing or trapping the microcatheter is reduced and it is possible to perform a more durable injection than with glue and to increase the volume of embolic agent injected.

Embolization is now completed in 15 patients and a complete occlusion was obtained in 2 patients (13%). The percentage of occlusion was greater than 60% in 14 out of 15 cases (93%). Additional data will be obtained at the end of our study (analysis of 50 patients and completion of endovascular treatment in all cases). Then, the percentage of complete occlusion will be more accurately defined and in case of incomplete occlusion a precise knowledge of the percentage of occlusion and of the complementary treatment will be available. Results recently presented by J. Moret et Al⁴ showed that the rate of complete occlusion after embolization with Onyx alone is greater than with glue.

With regard to procedural complications of the technique, four acute post-embolization hemorrhage (APEH) were reported in our series. One patient died and three patients are neurologically impaired. Overall the rate of APEH was 8% per patient and 4% per session. As was previously outlined by L. Picard et Al⁴, spontaneous acute post-embolization hemorrhage (APEH) after AVM embolization is observed independent of the therapeutic agent used. In the review of Picard et Al⁴, the frequency of bleeding after embolization with different embolic agents is 4.8%. Regarding glue embolization, APEH was observed in 8.2% of cases. In the clinical series of L. Picard et Al⁴, the incidence of APEH was 3.1%. In the series of Debrun et Al⁵, the risk of delayed hemorrhage with histoacryl was 11% per patient and 3.9%

per session. Overall the rate of delayed hemorrhage after glue embolization is in the literature between 3.1 to 11 % per patient. The percentage of hemorrhagic complications observed with Onyx in our series is thus close to the percentage reported by other investigators using glue.

Different hypotheses have been made to explain APEH: inappropriate venous occlusion of partially embolized AVM, increased pressure in feeding arteries as a result of embolization, normal perfusion pressure break-through, hyperemia of normal brain or redistribution of cerebral blood flow into adjacent regions, venous thrombosis secondary to stasis caused by substantial obliteration of the AVM, inflammatory reaction or mural necrosis induced by the embolic material, ischemic softening of tissue around an abnormal blood vessel which bled under pressure and intranidal rupture of aneurysm⁴.

The factors associated with the risk of APEH in our series are difficult to analyze due to the small number of patients. Only one out of the four patients had a previous hemorrhage. APEH was observed in AVMs having different sizes. Venous drainage was superficial (1 case) or deep and superficial (3 cases). During injection no venous passage of Onyx was observed and no stagnation was observed in the venous drainage after the treatment. Venous factors are then probably not responsible of our cases of APEH. The volume of Onyx injected was relatively large in two out of four cases (4.2 and 5.5 ml) but smaller in the two other cases (0.6 and 1.5 ml). The duration of the injection was in all cases greater than 30 minutes (30, 35, 52 and 70 minutes) but the mean duration of injection in the series was 34 minutes. The techniques used to withdraw the microcatheter was different in the different cases of APEH. Finally it is difficult to know if the factors associated with APEH after embolization with glue and Onyx are different. Venous factors are probably less important with Onyx than with glue. On the other hand, due to the fact that the duration and volume of injection are more important with Onyx, the hemodynamic changes are probably more important with Onyx than with glue. For this reason, waiting for a more precise analysis of APEH after Onyx embolization, it is probably important to avoid too important hemodynamic changes during the session of Onyx embolization by performing staged ses-

sions of embolization and by limiting the volume of Onyx injected per session. Additional research is needed before more definitive recommendations can be made.

As was previously outlined by Picard et al⁴, the only way to improve the outcome of patients with APEH is emergency craniotomy with evacuation of the hematoma and possibly resection of the residual nidus. In our cases, one patient was not operated on and died and the others were surgically treated and are now alive with neurological sequelae.

Four non-hemorrhagic complications were monitored in our series: three cerebral ischemia and one spinal cord ischemia. Neurological deficits were transient in two cases and permanent in two cases. The mechanism of the spinal cord ischemia is at the present time controversial and will be the matter of a specific publication.

Overall, the mortality of the treatment was 2% and the morbidity 10%. These percentages are close from those reported with glue⁸⁻⁹. Probably the percentage of morbidity and mortality is partially a reflection of the learning

curve in the use of a new product and will decrease along the time.

Conclusion

Preliminary results of a prospective, multicentric study dealing with embolization of brain AVMs are reported. Forty-eight⁴⁸ out of the 50 included patients were analyzed at the time of writing and treatment was completed in 15 out of 48 patients. Based on the percentage of complete occlusion and the percentage of occlusion of incompletely treated AVMs, embolization with Onyx seems to be efficient. The recent results presented by J. Moret et al³ confirmed the great efficacy of Onyx in the treatment of brain AVMs.

Acute post embolization hemorrhage was observed in 8% of patients. This percentage is close from what is observed with glue. In order to reduce the percentage of hemorrhagic complications, the occlusion of the nidus with Onyx should be progressively attained by staged sessions, and limitation of volume and duration of Onyx injection.

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Laurent Pierot, MD
Service de Radiologie
Hôpital Maison-Blanche
45, rue Cognacq-Jay
51092 REIMS cédex, France
Tel: 0326787566
Fax: 0326787594
E-mail: lpierot@chu-reims.fr