Endovascular treatment of brain arteriovenous malformations using onyx: Results of a prospective, multicenter study

L. Pierot a,*, A.-C. Januel b, D. Herbreteau c, X. Barreau d, J. Drouineau e, J. Berge d, N. Sourour f, C. Cognard b

a Department of Radiology, hôpital Maison-Blanche, 45, rue Cognacq-Jay, 51092 Reims cedex, France
b Department of Neuroradiology, hôpital Purpan, Toulouse, France
c Department of Neuroradiology, hôpital Bretonneau, Tours, France
d Department of Neuroradiology, CHU de Bordeaux, Bordeaux, France
e Department of Radiology, CHU de Poitiers, Poitiers, France
f Department of Neuroradiology, hopital Pitié-Salpêtrière, Paris, France

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Summary
Background and purpose. — To evaluate the safety and efficacy of onyx for embolization of brain arteriovenous malformations (BAVM).
Methods. — A prospective, multicenter study was conducted in France to evaluate embolization of BAVM with onyx. From May 2003 to March 2005, 50 patients (26 females, 24 males; mean age: 34.8 years, range: 16–64 years) were included. Clinical presentation was hemorrhage in 22 patients (44.0%), seizures in 16 patients (32.0%), headaches in six patients (12.0%) and progressive neurological deficit in two cases (4.0%). Four patients were asymptomatic (8.0%).
Results. — One hundred and forty-nine sessions of embolization were performed: one to eight sessions/patient with a mean of 3.0 sessions. One hundred and sixteen sessions (77.9%) were performed with onyx, 20 sessions (13.4%) with glue and 13 sessions (8.7%) with onyx and glue. Symptomatic acute postembolization hemorrhage (APEH) was observed in four cases (8.0% per patient). At 1 month, morbidity and mortality related to the treatment were of 8% and 2%, respectively. Complete BAVM occlusion was obtained in 8.3% of cases. In the remaining cases, occlusion rate was between 99 and 80% in 56.3% of patients, 79 and 60% in 16.7%, and less...
Introduction

The management of brain arteriovenous malformations (BAVM) is usually based on a multidisciplinary approach associating surgery, radiosurgery and embolization [1]. Indications for treatment are based on clinical presentation, patient characteristics including age and anatomic features. The goal of the treatment is primarily to eliminate the risk of bleeding which can be obtained only by complete obliteration of the nidus with complete occlusion of the arteriovenous shunts. The management of BAVM is still a matter of controversy including the indications of treatment in unruptured AVM, the place of embolization in the whole treatment and the way embolization has to be performed.

In recent years, techniques of embolization were greatly modified by the appearance of a new liquid embolic agent, onyx (EV3, Irvine, CA). Onyx is a radiopaque, non-adhesive embolic fluid which precipitates upon contact with blood. Onyx was proposed for the treatment of BAVM [2–8], dural arteriovenous malformations [9,10] and other conditions [11]. Several single center, retrospective series reported by very skilled teams have recently presented a preliminary analysis of clinical and anatomic results of embolization of BAVM with onyx [2–8]. In these series, an angiographic cure of the BAVM was obtained in 16 to 53.9% of cases. We report the first prospective, multicenter series dealing with embolization of BAVM with onyx.

Patients and methods

Study protocol

A prospective, multicentric study was conducted in seven french neurointerventional centers (Angers, Bordeaux, Paris - La Salpêtrière, Poitiers, Reims, Toulouse, Tours). Patients harbouring BAVM treatable by endovascular approach were included if the treatment was partially or completely performed using onyx. The protocol was approved by the ethics committee of Reims and informed consent was obtained from all patients.

Entry criterion was BAVM not previously treated whatever the clinical presentation and the location. In each center, indication for treatment and its modality (surgery, radiosurgery, endovascular treatment or associated techniques) was decided on a case-by-case basis by a local multidisciplinary team including neurosurgeons, neuroanesthesiologists, neurologists and neuroradiologists. The use of onyx or glue was decided on a case-by-case basis by each interventional neuroradiologist.

Exclusion criteria were age under 18, pregnancy and inability to give informed consent. The rationale for selecting the endovascular treatment (EVT) as the first line treatment option was not requested in the database. However, it should be emphasized that in most centers in France, EVT is usually proposed as the first line treatment in BAVM followed by surgery or radiosurgery in case of incomplete treatment.

Center experience

For all centers participating to this study, preliminary experience with the treatment of BAVM with glue was required. On the contrary, no preliminary experience with the treatment of BAVM with onyx was required and in most centers, patients included in this series were the first patients harbouring BAVM treated with onyx.

Patients

From May 2003 to March 2005, 50 patients (26 females, 24 males; mean age: 34.8 years, range: 16–64 years) were included.

Clinical presentation was haemorrhage in 22 patients (44.0%), seizures in 16 patients (32.0%), headaches in 6 patients (12.0%) and progressive neurological deficit in two cases (4.0%). Four patients were asymptomatic (8.0%).

BAVM morphology

BAVM were classified according to location (hemispheres, corpus callosum, basal ganglia and thalamus and cerebellum), size (<3 cm, 3 to 6 cm, >6 cm) and venous drainage (deep, superficial or deep and superficial; unique or multiple).

Endovascular procedure

Procedures were performed with patients under general anesthesia. Steps of the procedures were superselective catheterization of the nidus using a dimethyl sulfoxide (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 onyx injection, 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 s) 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 was stopped for 2 min. In case of venous passage, injection was briefly stopped. Various techniques were used to withdraw the microcatheter (slow continuous traction, fast traction).
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Immediate outcome and patient follow-up

Technical conditions of the procedure were reported including the type of agents used (onyx, glue or both), the duration of onyx injection and volume injected.

All technical and clinical complications were reported and independently analyzed by an interventional neuroradiologist (LP). Clinical outcome was evaluated by using the modified Rankin scale (mRS), one month after the end of all endovascular procedures and before the complementary treatment when needed. Anatomical results were evaluated 1 month after the end of the endovascular procedures. In case of complete occlusion, control angiogram was performed 6 to 12 months after the end of the treatment. In case of incomplete occlusion, further management of the patient was reported.

Results

AVM population

The locations of the AVM were:

- in the cerebral hemispheres in 43 cases (86.0%);
- in the corpus callosum in 3 cases (6.0%);
- in the basal ganglia and thalamus in 2 cases (4.0%);
- in the cerebellum in 2 cases (4.0%).

Size of the AVM was:

- inferior to 3 cm in 14 cases (28.0%);
- 3 to 6 cm in 31 cases (62.0%);
- inferior to 6 cm in five cases (10.0%).

Venous drainage was deep in nine cases (18.0%), superficial in 29 cases (58.0%) and deep and superficial in 12 cases (24.0%). Venous drainage was unique in 15 cases (35.0%) and multiple in 35 cases (70.0%).

Technical results

One hundred and forty-nine sessions of embolization were performed: one to eight sessions/patient with a mean of 3.0 sessions. The mean number of sessions was 1.1 in AVM <3 cm, 3.4 in AVM 3 to 6 cm and 6.5 in AVM >6 cm. One hundred and sixteen sessions (77.9%) were performed with onyx, 20 sessions (13.4%) with glue and 13 sessions (8.7%) with onyx and glue.

Duration of injection of onyx was 5 to 70 min with a mean of 35 min.

The volume of onyx injected per session was 0.08 to 6 ml with a mean of 1.6 ml.

Technical problems

Perforation or dissection of the feeding pedicle without bleeding was observed in six cases. Withdrawal of the microcatheter was impossible in four cases (by fast traction in three cases and slow traction in one case). Rupture of the microcatheter was reported in two cases and cervical dissection (created by the guiding catheter) in one case. When the microcatheter was left in place (withdrawal impossible or rupture), antiplatelet medication was given for several weeks to avoid thromboembolic complications.

All the technical problems had no clinical impact.

Clinical complications

Acute postembolization haemorrhage (APEH) was observed in seven patients (4.7% per session). In all cases, APEH occurred in patients harbouring BAVM treated in several sessions of embolization.

In five cases, haemorrhage occurred after a session of onyx treatment (4.3% per session), in one case after a session of glue treatment (5.0% per session) and in one case after a session of glue and onyx treatment (7.7% per session). In all cases, APEH occurred in the hours following embolization. In three cases, bleeding was not associated with any clinical modification. Symptomatic acute postembolization hemorrhage was encountered in four patients (8.0%). In two cases, hematomas were surgically removed. Postoperatively both patients had a severe neurological deficit (modified Rankin scale [mRS] = 5). The other two patients did not undergo surgery. In one case, as a large portion of the nidus was not embolized, the neurosurgeon was cautious regarding the possibility of having good control of the operative patient’s bleeding. This untreated patient eventually died due to brain compression and intracranial hypertension. The other patient had a minor neurological deterioration related to the bleeding.

Non hemorrhagic deficits were encountered in five patients, after onyx treatment in four cases and after onyx and glue treatment in one case. In two patients postoperative deficit was mild (mRS1). In the other three patients, postoperative mRS was 2, 3 and 4, respectively.

Clinical outcome at 1 month

Thirty-day treatment related morbidity (mRS 3 to 5) was 8% (four patients) and 30-day treatment related mortality was 2% (one patient, see above). Another patient harbouring a ruptured AVM was mRS grade 5 before the treatment. The treatment of the AVM was performed without technical or clinical complications. He died during the follow-up period due to the severity of the initial bleeding. Finally the overall rate of mortality in this series was 4.0% (two patients).

Anatomical results

Results of the endovascular treatment were evaluated in the 48 surviving patients. Percentage of occlusion was 100% in four cases (8.3%), 80 to 99% in 27 cases (56.3%), 60 to 79% in 8 cases (16.7%) and less than 60% in 9 cases (18.7%).
Subsequent treatment

Out of the 44 patients with incomplete occlusion after embolization, 37 were proposed for radiosurgery. Four patients refused a complementary treatment and 3 patients with a clinical worsening after embolization were at the present time not proposed for a complementary treatment.

Discussion

The primary goal of the treatment of BAVM is to prevent bleeding and for this purpose complete exclusion of the AVM is necessary. Various techniques are available to treat BAVM (surgery, radiosurgery and embolization) and an association of techniques is often necessary to obtain a complete cure of the AVM. Embolization is often the first step of the treatment to obtain a complete occlusion of the nidus or to reduce its size for a subsequent treatment (surgery or radiosurgery). As previously outlined by Mounayer et al. [7], there are grossly two strategies of treatment of patients harbouring BAVM. The first associates embolization and surgery and the goal of embolization is to minimize intraoperative blood loss. The second was used in the present series and try to optimize results of embolization. The goal is to obtain a complete occlusion of the nidus by embolization alone or to occlude as much as possible the nidus to facilitate further treatment (surgery or radiosurgery). For the second therapeutic strategy, a permanent embolic agent has to be used and the quality of the results is directly linked to the quality of the embolic agent. As the use of onyx for BAVM was in most teams in our study the first experience with this product, the strategy of embolization was mostly to reduce sufficiently the size of the BAVM to allow complementary treatment.

Various embolic agents have been proposed for the treatment of brain AVM including particles and cyanoacrylates. Onyx (EV3, Irvine, CA) is a biocompatible agent made of a mixture of ethylene-vinyl alcohol copolymer (EVOH) and DMSO. As the process of solidification of cyanoacrylates is based on polymerization, onyx will solidify through a precipitation process. Subsequently, the injection of onyx inside the nidus is slower, is more controllable and will theoretically allow a more important filling of the BAVM nidus. Onyx seems then to be singularly appropriated to the second strategy of treatment. Preliminary series [2–8], Table 1 in experienced teams have shown that endovascular treatment of BAVM with onyx is feasible associated with a high rate of complete occlusion (16 to 63.6%). The rate of hemorrhagic complications in onyx embolization is between 5.9 to 16.7%. Morbidity and mortality related to onyx embolization of BAVM are, respectively, between 4.6 to 16.7%, and 0 and 3.2%. In our series, very similar results were obtained including symptomatic hemorrhagic complications in 8.0% of patients, morbidity related to the treatment in 8.0% and mortality related to the treatment in 2.0%. Thus the safety results of embolization of BAVM with onyx are homogeneous from one series to another.

Is the safety of onyx different from those of cyanoacrylates? Several series have reported for more than 35 years results of the embolization of BAVM with isobutyl-cyanoacrylate (IBCA), N-butyl-cyanoacrylate (NBCA) or more recently Glubran. Several factors make accurate evaluation of the safety of cyanoacrylates very difficult:

- the use of different embolization agents in the same series without subgroup analysis;
- a great variety of techniques used from one series to another even for cyanoacrylates embolization;
- very rapid evolution of catheter technology and changes in operator experience and skill along with technological improvement;
- the very different methods of patient selection;
- the different goals of embolization (see above).

To analyze the results of cyanoacrylates embolization, the series published after 2000 were selected in order to reduce heterogeneity regarding techniques used ([12–18], Table 2). Series in which sufficient data were not provided to analyze safety were not included in the analysis. According to Table 2, the morbidity and mortality rates after embolization of BAVM with cyanoacrylates were 3.0 to 7.9% and 0.8 to 7.0%, respectively. Then the mortality rate seems to be in the same range for both onyx and cyanoacrylates and morbidity is slightly higher after onyx embolization. However, onyx and cyanoacrylates series are not directly comparable as the number of patients in cyanoacrylates series is generally higher than in the onyx series. Moreover, cyanoacrylates series are reporting results of a more stabilized technique as onyx series are generally reporting preliminaty experience with a new product as in our series.

The most frequent complication after embolization of BAVM with onyx or glue is hemorrhagic. In all but one onyx

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**Table 1** Clinical and anatomical results of the endovascular treatment of BAVM using onyx.

<table>
<thead>
<tr>
<th>N</th>
<th>Hemorrhagic complications (%)</th>
<th>Morbidity (%)</th>
<th>Mortality (%)</th>
<th>Complete occlusion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perez-Higuera et al., 2005</td>
<td>45</td>
<td>8.9</td>
<td>15.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Tevah and Huete, 2005</td>
<td>24</td>
<td>16.7</td>
<td>16.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Song et al., 2005</td>
<td>50</td>
<td>6.0</td>
<td>10.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Van Rooij et al., 2007</td>
<td>44</td>
<td>6.8</td>
<td>4.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Weber et al., 2007</td>
<td>93</td>
<td>—</td>
<td>12.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Mounayer et al., 2007</td>
<td>94</td>
<td>8.5</td>
<td>8.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Katsaridis et al., 2008</td>
<td>101</td>
<td>5.9</td>
<td>8.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Present series</td>
<td>50</td>
<td>8.0</td>
<td>8.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

BAVM: brain arteriovenous malformations; N: number of patients.

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series, hemorrhagic complications are reported in approximately 8.0% of cases. In cyanoacrylates series, the rate of hemorrhagic complications was between 3.1 to 13.0%. In our series, the rate of hemorrhagic complications after embolization with onyx (4.3% per session) is similar to the rate with glue (5.0% per session). As was previously outlined by Picard et al. [19], spontaneous acute APEH after AVM embolization is observed whatever the therapeutic agent used. In this review, the frequency of bleeding after glue embolization is 8.2%. 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;
- hyperaemia 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;
- intranidal rupture of aneurysm [19].

The factors associated with the risk of intraoperative or postoperative bleeding in our series are not analyzable due to the small number of patients in each subgroup.

There is several ways to evaluate the efficacy of an embolic agent in the treatment of BAVM: percentage of BAVM completely occluded by embolization alone, mean occlusion rate in a population of patients harbouring BAVM, BAVM amenable to radiosurgery after embolization. Whatever the method of evaluation used, the efficacy of embolization in a specific series is strongly related to patient’s and AVM characteristics. According to the percentage of BAVM completely cured by embolization alone, results are different with cyanoacrylates and onyx as complete occlusion was obtained with cyanoacrylates in 5.6 to 30% of cases and with onyx in 8.3 (our series) to 63.6%. Due to their different way of solidification, injection time can be longer with onyx than with cyanoacrylates resulting in a higher volume injected per session which is the explanation for the higher rate of complete occlusion with onyx. The relatively low percentage of complete occlusion in our series is probably due to the fact that it was for all centers the first experience with endovascular treatment of BAVM with onyx. Then the final goal of the embolization was mostly as with glue to reduce sufficiently the size of the BAVM to be able to conduct a safe and efficacious complementary treatment singularly radiosurgery.

### Conclusion

In this first prospective, multicenter series, onyx proved to be suitable for BAVM embolization. According to the rate of hemorrhagic complications, morbidity and mortality, the safety of embolization with onyx seems to be similar to cyanoacrylates. Further multicenter studies conducted in experienced centers and including a larger number of patients are needed to precisely evaluate the efficacy of onyx.

### Conflicts of Interest

This registry was financially supported by EV3 France. L. Pierot is consultant to EV3 France.

### References


