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Preembolization Functional Evaluation in Brain Arteriovenous Malformations: The Superselective Amytal Test

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Purpose: To describe our experience with the use of Amytal injected through a superselective catheter prior to planned embolization of cerebral arteriovenous malformations. **Materials and Methods:** 109 superselective tests were performed with 30-mg injections of Amytal. All patients were evaluated by both clinical examination and EEG. **Results:** Twenty-three of these tests were positive. There were no prolonged neurologic complications of the Amytal test. We also examined the value of EEG monitoring compared to clinical monitoring during the Amytal test. Of the 23 positive Amytal tests, only 12 showed a change on clinical exam (52%). This meant that almost half of the positive Amytal tests would have been falsely called negative (false negative rate of 10%). There were also three positive Amytal tests with changes on clinical examination without any change on EEG. **Conclusion:** The superselective Amytal test can be done safely as part of the interventional neuroradiologic procedure. Clinical and EEG monitoring of the patient are essential.

Index terms: Arteriovenous malformations, cerebral; Embolism, therapeutic blockade; Interventional neuroradiology, provocative testing

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A selected group of patients with arteriovenous malformations (AVMs) benefit from embolization prior to surgical removal of the AVMs (1). Because the AVMs may be accompanied by extensive gliosis (2), embolization may be done in some cases without compromise of blood flow to functional brain tissue. With the development of microcatheters over the past several years, it has become possible to selectively catheterize small second- and third-order branch vessels off the circle of Willis. This allows the interventional neuroradiologist to deliver embolic agents to precise locations within the cerebral vascular system (1, 3), thus making the goal of preserving all normal brain tissue during the embolization more attainable. Preembolization superselective angiography (4) aids in this goal, giving anatomic, dynamic, and functional data about the vascular territory of the cerebral vessel catheterized. To improve upon the functional information available intra-arterial injection of Amytal (amobarbital, a short acting barbiturate, Eli Lilly, Indianapolis, IN) as part of our evaluation of cerebral vessels prior to embolization.

Intraarterial injection of Amytal was described by Wada and Rasmussen (5) as a method for evaluation of cerebral function within the vascular distribution of an injected vessel. The carotid artery Amytal injection was done primarily to determine which cerebral hemisphere was dominant for language function. This information was used to help plan ablative brain surgery in patients with intractable seizures. With the development of microcatheters, not only could embolization be done more selectively, but the Amytal test also could be done much more selectively than origi-

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nally described by Wada and Rasmussen (5). The use of a catheter within a posterior cerebral artery to selectively test the effect of Amytal on one hippocampus has been described (6). Injection of either Amytal or lidocaine to detect feeding vessels to the spinal cord in animals (7) and man (8) has been described. An earlier report by one of the authors (F.V.) also suggested the usefulness of this superselective Amytal test (4) prior to embolization of AVMs of the brain. The present manuscript is the first comprehensive report of the use of this superselective test prior to AVM embolizations.

The other purpose of this manuscript is to describe how the patients were evaluated during the superselective Amytal test. All of our patients undergoing superselective Amytal testing and embolization were monitored by a neurologist throughout the procedure. This included not only monitoring of the clinical examination, but also the electroencephalogram (EEG). The impact of this monitoring, in particular monitoring the EEG data, will be discussed along with our experience with the superselective Amytal test over the past 36 months. A subsequent manuscript will present the results of embolization of these patients.

Materials and Methods

The data from 33 patients who underwent embolization of their AVMs during the last 36 months were analyzed retrospectively. The patient population was limited to patients with cerebral AVMs who were awake during the embolization. This limitation allowed for maximum opportunity to evaluate any changes in the patient produced by the Amytal injection. All 33 patients had supratentorial brain AVMs. Twenty-two patients were female, 11 were male (see Table 1). The mean age was 32 years (16–73 yr).

All patients were evaluated by a neurologist prior to embolization and a baseline EEG was obtained. The EEG was presented on a continuous 16-channel paper record and the EEG data was analyzed by a computer. The data from the computer were presented as a group of color-coded brain maps showing relative quantity of EEG activity in slow frequency range (delta activity, <4 Hz), slightly slow range (theta activity, 4–8 Hz), normal fast range (alpha activity, 8–13 Hz), and fast range (beta activity, >13 Hz). These maps were updated every 2.5 sec (see Fig. 1).

Focal neurologic deficits, whether produced by focal ischemia or transiently by Amytal injection, may be clinically detected or may produce focal EEG changes (see Fig. 1). These EEG changes show a slowing in the rhythm of the brain waves which may be reflected by a loss of the normal fast (alpha) activity or an increase in the slow (delta) activity, with the former thought to be more sensitive for minor changes than the latter (9, 10). On the computer-generated brain maps, focal changes in EEG activity were best seen as a change in symmetry in the brain maps. in particular there were decreases in alpha activity and increases in delta activity (See Fig. 1C). The computer analysis of the EEG was an attempt to make real time evaluation of the patients' EEGs easier and make subtle changes more evident.

TABLE 1: Distribution of AVMs

Right Hemisphere	Left Hemisphere
15	18
Frontal Lobe	5
Frontal-temporal	2
Frontal-parietal	3
Temporal	9
Temporal-parietal	5
Parietal	5
Parietal-occipital	3
Occipital	0
Basal ganglia	1

All patients were awake throughout the embolization. Sedation was used sparingly to limit its effect on the clinical examination and EEG. Sedation was generally obtained with Versed (Roche Dermatologics, Nutley, NJ) plus a short acting narcotic (such as Fentanyl, Elkins-Sinn, Inc, Cherry Hill, NJ). Droperidol (American Regent Laboratories, Inc, Shirley, NY) was found to produce more diffuse slowing of the EEG than the other sedating drugs and was generally avoided. All patients were monitored throughout the procedure by both EEG and clinical examination. The EEG data were then reevaluated by at least two neurologists at a weekly EEG reading session.

The superselective angiography was carried out through a coaxial catheter system that was placed through a sheath in the femoral artery. A microcatheter (either a Tracker catheter, Target Therapeutics Inc., San Jose, CA or a Balt catheter, Balt, Montmorency, France) was positioned in the brain AVM feeder and digital superselective angiography was performed. This provided anatomical data (including the location of the catheter within the vessel, the anatomy of the AVM feeding vessel, the AVM nidus, adjacent cortical branches, and draining veins), as well as dynamic data (such as circulation) (Figs. 2 and 3). There have been previous reports of minor, reversible neurologic deficits following contrast injection (4, 8). Thus some functional transient or permanent) developed in any of these patients after contrast injection. This may have been because non-ionic contrast was used or because the digital equipment allowed use of contrast diluted with saline.

Prior to Amytal injection, the catheter was meticulously flushed with saline to clear any remaining contrast. This was done to prevent the precipitation of Amytal that may occur when mixed with contrast. Then, intraarterial injection of 30 mg of Amytal (diluted with normal saline to a concentration of 12.5 mg of Amytal per mL of saline, see

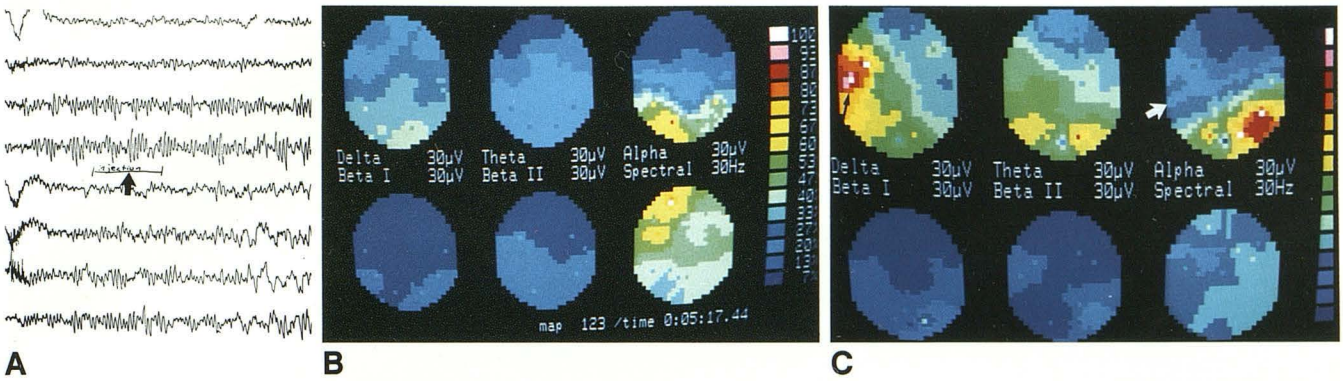

Fig. 1. Preembolization/functional embolization.

A, EEG during Amytal injection shows right hemisphere activity in the top four channels and left hemisphere activity in the lower four channels. The mark (*straight arrow*) denotes the time when the Amytal was injected. Note the loss of fast activity and the slow waves seen after Amytal injection in the lower four channels (left hemisphere).

B, Computerized mapping of brain electrical activity produced by computer analysis of EEG. The left side of the head is on the reader's left. This map shows symmetric activity.

C, Computerized mapping of brain electrical activity after Amytal injection. Note increased delta activity (*black arrow*) and decreased alpha activity (*white arrow*), on the left.

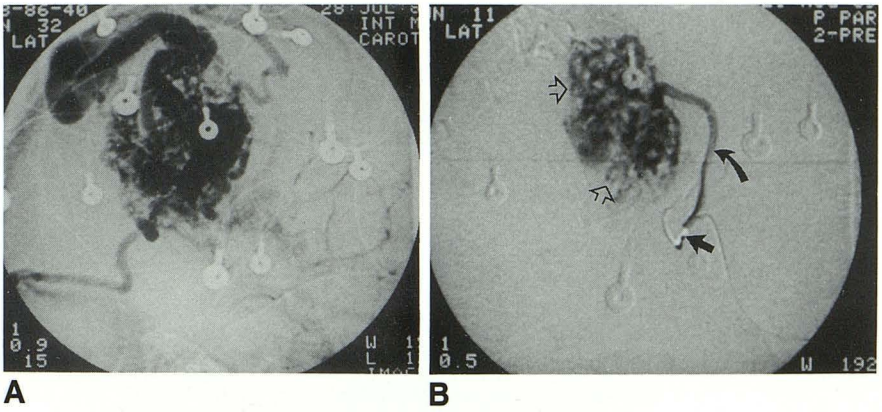

Fig. 2. Superselective catheterization.

A, Late arterial phase of right internal carotid angiogram (anterior to reader's right) shows a large parietal, arteriovenous malformation. Notice several EEG electrodes on the patient's skull.

B, Pre-Amytal superselective angiogram of a large arterial parietal feeder demonstrates the catheter tip (*straight arrow*), the arterial feeder (*curved arrow*) and a plexiform AVM nidus (*open arrows*). This angiogram was immediately followed by the injection of 30 mg of Amytal through the microcatheter.

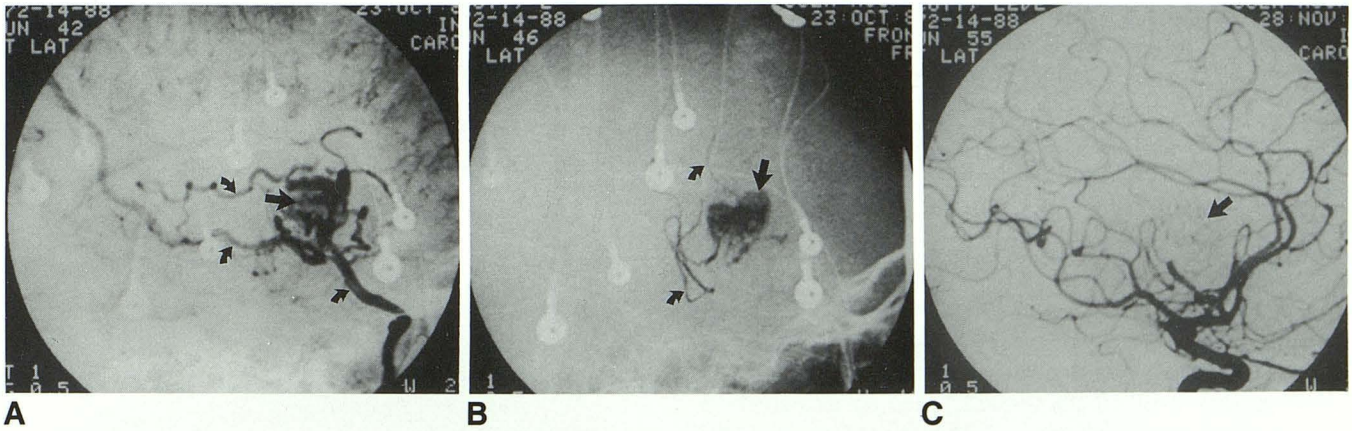

Fig. 3. *A*, Late phase of left lateral internal carotid angiogram (anterior to reader's right) shows a small inferior frontal AVM nidus (*straight arrow*) and several serpiginous cortical draining veins (*curved arrows*).

B, Superselective angiogram of main arterial feeder shows the AVM nidus (*straight arrow*) and several normal cortical branches (*curved arrows*).

C, Immediate postembolization left internal carotid angiogram shows successful endovascular obliteration of the AVM nidus (*straight arrow*) and preservation of normal cortical branches. Patient remained neurologically unchanged at the end of the procedure.

TABLE 2: Amytal dilution chart (250 mg vial)

Volume Used to Dilute Vial	Concentration	Osmotic Concentration (using water as the diluent)	Osmotic Concentration (using saline as the diluent)	Volume Injected[a]
2.5 mL	100 mg/mL (10% solution)	830 mOs/L[b]	1138 mOs/L	0.3 mL
20 mL	12.5 mg/mL (1.25% solution)	105 mOs/L	413 mOs/L[c]	2.4 mL

[a] Volume injected to give 30-mg dose.

[b] Standard Amytal dilution used for intravenous or intramuscular injection and Amytal dilution used by Wada and Rasmussen (5) for intracarotid injections.

[c] Dilution used at our institution for all Amytal intraarterial injections.

Table 2) was performed through the microcatheter. The rate of injection was similar to both the rate of injection of contrast (for the angiogram) and the planned injection rate for the embolic material. If no change in the baseline clinical neurologic examination or EEG was detected, the Amytal test was considered negative and embolization of the AVM was carried out.

The results show that the number of Amytal tests exceeds the number of patients. This is because many of the AVMs had several major feeders, each one requiring a superselective Amytal test. In addition, these large feeding vessels often required several embolizations, and, in that case, a repeat superselective Amytal test was frequently needed.

Results

There were a total of 109 Amytal tests done. The vascular distributions of the vessels studied by Amytal tests were as follows: anterior cerebral artery, 13 patients; middle cerebral artery, 32 patients; posterior cerebral artery, 18 patients. The Amytal test was considered negative if there were no changes observed on either the EEG or the neurologic exam following Amytal injection. There were 86 negative Amytal tests (79% of the total tests done). The Amytal test was considered positive if either the EEG or clinical exam or both were changed following Amytal injection. In all cases, any changes following Amytal were evident within 1 minute following injection, and the focal effects of Amytal had all dissipated by 10 minutes into the test. There were 23 positive Amytal tests. Of these positive tests, 11 consisted of changes limited to the EEG, with no change on clinical exam (48% of the positive Amytal tests). The remaining 12 positive Amytal tests were positive on clinical examination. Of these, nine were positive on EEG and clinical examination and three were positive by clinical examination only (see Table 3).

Discussion

During this study, a total of 109 Amytal tests were performed, without evidence of any neurologic deficits that did not clear spontaneously within 10 minutes (as the Amytal effect dissipated). Although we had no neurologic complications in our superselective Amytal injections, there have been previous anecdotal reports of long-term neurologic dysfunction following Amytal injection (including deficits due to hemorrhage or possibly to infarction of brain tissue). Three possible explanations for these reported complications include: 1) damage to the artery due to rapid injection, 2) damage of the vessel due to osmotic shock, and 3) precipitation of Amytal with occlusion of a vessel. As noted above, the Amytal injection attempted to reproduce the injection of contrast and embolic material. This not only served to protect the vessel from sudden pressure changes associated with rapid injection (none of the patients in our series had any evidence of vascular disruption following the injection) but also should most accurately duplicate the flow pattern of the embolic agent (as well as the angiographic contrast). This should assure the most consistent comparison between the portion of cerebral tissue affected by Amytal and the

TABLE 3: Amytal tests

Total Amytal tests	109
Number of positive Amytal tests (changes in exam *or* EEG)	23
Positive Amytal tests with changes on clinical exam	12 (52%)
Positive Amytal tests with changes on EEG but not the clinical exam	11 (48%)
Negative Amytal tests	86
Permanent neurologic changes following Amytal	0

portion of cerebral tissue that would be affected by an embolization.

We felt that adequate dilution of Amytal was important. The standard concentration of Amytal used for intramuscular or intravenous injection is 100 mg/mL (10%), obtained by dissolving the 250-mg vial of Amytal in 2.5 mL of diluent. This is also the concentration used by Wada and Rasmussen (5) in their intracarotid injections. The osmolality for such a solution is 830 mOs/L (if water is used to mix the solution) to 1138 mOs/L (if normal saline, the most readily available diluent in the angiographic suite, is used). This is approximately three times the normal serum osmolality of 285 mOs/L. By comparison, the mixture of contrast and saline we used for angiography had a tonicity of only approximately 530 mOs/L. The Amytal solution we have used (12.5 mg/mL) had a total tonicity of 413 mOs/L when Amytal was mixed with normal saline (11) (see Table 2). Although we have no proof that the more concentrated solution would induce vascular damage, we think that it is prudent to inject an Amytal solution with a more physiologic osmotic concentration.

Finally, neurologic dysfunction could be produced by precipitated Amytal that could occlude small vessels in the brain. Although embolization of the vessel was generally planned, we did not wish to do this during Amytal testing. To reduce the chance of precipitation of Amytal, the catheter was carefully flushed of any angiographic contrast. The mechanism of the reported possible precipitation of Amytal when it is exposed to contrast is unclear. It could relate to changes in the pH of the Amytal solution when the more acidic contrast comes in contact with the more basic Amytal solution. It is known that Amytal may precipitate if its pH is lowered excessively. Since the extent to which Amytal is prone to precipitate increases with higher concentrations, the use of a dilute Amytal solution will also reduce the chance of precipitation (11). It should be noted that use of a dilute Amytal solution requires a larger injection volume for the same dose than if a higher concentration is used. However, if injected slowly, this should not create a problem and a larger volume might assure more complete filling of the selected vessel.

The standard dose of Amytal for internal carotid artery injection (for test of whole hemisphere function) at our institution is 125 mg. Similarly, Wada and Rasmussen (5) described using 150–200 mg of Amytal for injection into the common carotid artery. To fill only the tissue supplied by a feeding vessel to an AVM, considerably less than this amount of Amytal should be required. However, the feeding vessel to an AVM may be associated with a large blood flow, so the goal was to select a dose that would allow delivery of the drug to all of the tissue supplied by an AVM feeding vessel. At the same time, it was desirable to limit the dose in order to prevent drowsiness in the patient, even if repeated Amytal injections became necessary. Drowsiness could limit the clinical examination, as well as produce diffuse slowing in the EEG. One of the authors (F.V.) previously described the use of 20 mg of Amytal for superselective Amytal injection (4). For the present study, the dose of Amytal chosen was increased slightly to 30 mg to assure more complete filling of the vessel.

The 23 positive Amytal tests showed that the selected dose of Amytal was large enough to produce an effect if Amytal was injected into vessels serving functional brain tissue. However, the dose did not appear to be too large, as none of the procedures had to be discontinued due to patient drowsiness. Of the 23 positive Amytal tests, 11 had changes on EEG without a change in their clinical examination. Thus, without EEG monitoring of the patients, almost half of the positive Amytal tests would have erroneously been called negative. Or to state this another way, if the Amytal test had only used data from the clinical examination, 11 of the 109 total Amytal tests would have been falsely labeled negative (a false negative rate of 10%). Based on these findings, we conclude that EEG monitoring was essential in evaluating the Amytal test. Our primary goal was to identify positive Amytal tests, even those with changes limited to EEG findings, in order to help make better decisions as to which vessels could be embolized without causing neurologic complications. Even if these neurologic "complications" were to be limited to a slowing of the EEG, it could potentially decrease the patient's neurologic reserve, produce subtle subclinical changes in the patient (12), or make him more susceptible to clinically evident neurologic dysfunction following surgical removal of the AVM.

Note that clinical evaluation of the patient was also needed to assure that all the positive Amytal tests would be identified, since there were three positive Amytal tests that showed changes on the clinical examination but had no changes identifiable on EEG. This may have been a result of

the Amytal on subcortical brain tissue (with little change evident on EEG) or the Amytal effect may have been limited to a very small, but exquisitely eloquent, region of cortex (thus creating a change that was too small to be reflected on EEG, but which was evident clinically).

Preembolization functional testing was carried out in all of our patients using Amytal. It has been suggested that lidocaine injected intraarterially might be better than Amytal in identifying functional white matter within a vascular distribution (7, 8). However, Amytal, which has its maximum effect at or near synaptic connections, does apparently produce some effect within myelinated neuronal tracts. Furthermore, most of the AVMs involved cortical regions of the brain to some extent. Finally, because of lidocaine's known potential for inducing seizure activity in cortical tissue, we felt that Amytal was a safer agent than lidocaine. For all these reasons, functional test injection was done with Amytal rather than lidocaine.

Conclusion

This article described our experience with the superselective Amytal test, with injection of 30 mg of Amytal through a microcatheter prior to embolization of an AVM to attempt to recognize the existence of vessels supplying normal brain tissue. Our findings were:

1. Injection of 30 mg of Amytal into a vessel can produce transient neurologic deficits if normal brain tissue is supplied by the vessel.
2. The test is safe. In 109 such injections, there were no adverse long term effects of the Amytal injection.
3. EEG is a valuable method in evaluating the patient following the Amytal test. Without EEG, almost half of the positive Amytal tests would have been called negative and there would have been a false negative rate of 10%.

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