Feasibility of the Superselective Test with Propofol for Determining Eloquent Brain Regions in the Endovascular Treatment of Arteriovenous Malformations

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Summary

The superselective test for determining eloquent brain areas, carried out prior to the embolization treatment for arteriovenous malformations (AVMs), is a tool contributing to increase the safety of endovascular procedures. Taking into account amobarbital unavailability, it was decided to carry out the present study to demonstrate the efficacy and safety of propofol as an alternative to amobarbital to perform this test.

A group of 58 patients were treated in 91 embolization sessions for brain AVMs using endovascular surgery between February 2006 and February 2011. The superselective test was performed prior to embolization with Histoacryl, using the intra-arterial administration of 20 mg propofol through a microcatheter positioned near the AVM nidus.

Ten (7.8%) of the 128 superselective tests were positive. Neurological deficits appeared immediately after propofol administration, lasted for one minute and disappeared after five minutes. Only one of the patients showing a negative test result developed neurological deficits after embolization, for 99.2% negative predictive value. Despite their positive test results, six patients were embolized and five developed post-embolization neurological deficits, for 83.3% positive predictive value. The test showed 83.3% sensitivity and 99.2% specificity.

The use of propofol to perform the superse-

lective test during brain AVM embolization is a safe and effective alternative to amobarbital, and may predict the occurrence of post-embolization ischemic complications.

Introduction

Endovascular treatment is a well-established AVM treatment option that is often combined with surgery or radiosurgery. The reported complete resolution of AVMs treated with endovascular procedures in a series of cases¹⁻⁵ ranges between 5% and 40%. In groups showing favorable angiographic features, the reported complete resolution rates reach 74%, compared to 40% for the entire series³. The reported complication rate varies between 3% and 25%^{2,6-8}. The permanent morbidity and mortality rates vary in the 3.8%-14% and 1.0%-3.7% ranges, respectively^{5,9}. Approximately 10% of brain AVM embolizations cause permanent neurological deficits¹⁰, and a large number of these deficits are caused by the embolization of branches emerging from the AVM and supplying the normal brain parenchyma^{5,7}.

Thus, the superselective test is an essential tool to prevent this problem by identifying any angiographically hidden irrigation of the normal brain parenchyma⁵. Usually, the superselective test for extra-axial target arteries is performed using lidocaine and the superselective

test for intra-axial target arteries is carried out using barbiturates such as amobarbital, although both agents have been used in both situations¹¹⁻¹⁷. One study reported that concomitant administration of amobarbital and lidocaine may improve the provocative test's sensitivity¹⁵. However, the safety profile of intracranial lidocaine has not been studied in detail.

In response to a global decrease in amobarbital availability, alternative agents have been tried to perform the Wada test. Some of these are methohexital (Brevital)^{18,19}, etomidate^{18,20} and propofol^{18,21-26}, which have yielded results similar to those obtained with amobarbital^{23,25}. Propofol is a widely available anesthetic comparable to amobarbital in terms of efficacy and safety. It has only a few adverse effects causing a transient deficit of neurological functions. There are a small number of reports on the use of propofol to perform the superselective test^{27,28}. This study deals with the efficacy and safety of the superselective test with propofol for determining eloquent areas in the treatment of brain arteriovenous malformations.

Materials and Methods

The study population consisted of all brain AVM patients evaluated between February 2006 and February 2011 at CIMEQ Hospital, from whom a sample of 58 patients was selected. This sample met CIMEQ's standardized criteria for treating endovascular brain AVMs. The patients went through 91 embolization sessions. The time between successive embolizations ranged between one and four months. All patients were evaluated before the procedure and informed consent was requested from them or their families in all cases to perform the superselective test with propofol and the subsequent embolization. Patients were notified of the use of propofol, and this procedure was approved by CIMEQ's Ethics Committee.

As a first step, a brain pan-angiography was performed using Seldinger's technique and local anesthesia to evaluate the AVM angio-architecture. Next, the diagnostic catheter was replaced by a 6 Fr guiding catheter using a 0035" guide wire 260-300 cm long, placing it in the internal carotid artery or the AVM's afferent vertebral artery. Then the AVM's afferent vessels were navigated with a Magic 1.5 microcatheter and a 0.009" microguide wire to catheterize the malformation pedicle and place the

microcatheter in a wedge position at the entrance to or within the nidus.

Subsequently, superselective angiography was performed using the microcatheter to verify its position in relation to the nidus. Prior to embolization, a superselective test was performed through the intra-arterial administration of 20 mg propofol using the microcatheter positioned near or within the nidus. Doses larger than those commonly used in the Wada test (10-15 mg intracarotid) were used to achieve a transient neurological deficit without producing drowsiness or confusion that could interfere with the neurological assessment.

A neurological evaluation including the examination of cranial nerves, taxis dynamics, segmental muscle strength, superficial and deep sensitivity, language, gnosis, praxis, immediate memory, calculation and visual function was performed by a neurologist. This evaluation was carried out just before, one minute and five minutes after propofol administration. In case of a positive test result (indicating focal neurological deficit), another arterial pedicle was catheterized. The same test was repeated if prior to administering the embolization substance there was evidence of the microcatheter having changed its position. Then the embolization was performed without general anesthesia using Histoacryl. Digital subtraction angiography was performed with monoplane units (Philips Integris and Siemens Artist).

Results were expressed as percentages, and sensitivity and specificity were calculated as measures of the test's efficacy. The positive (PPV) and negative predictive value (NPV) of the superselective test were also determined. The safety of propofol utilization was evaluated following a detailed recording of any adverse effect of its administration.

Results

Fifty-eight patients were treated and 91 embolization sessions of arteriovenous malformations were carried out. Tables 1 and 2 show the demographic, clinical and angiographic characteristics of the treated patients. All patients underwent a superselective test with propofol in each session, 128 tests being performed, of which ten (7.8%) were positive. In all cases, the neurological deficit appeared immediately after propofol injection, remained for one minute, and disappeared within five minutes.

Table 1 Clinical and demographic characteristics and results of CT scans of the population of patients with treated arterio-venous malformations.

Variable	Number	Percentage
Age (years)		
10 - 20	19	32.7
21 - 30	12	20.6
31 - 40	15	25.8
41 - 50	10	17.2
51 - 70	2	3.4
Sex		
Male	36	62.1
Female	22	37.9
Racial Morphotype		
White	31	53.4
Black	19	32.7
Mixed race	8	13.8
Associated Diseases		
Arterial hypertension/ high blood pressure	9	15.5
Epilepsy	5	8.6
Bronchial asthma	2	3.4
Onset Clinical Symptoms		
Headache	27	46.5
Seizures	17	29.3
Loss of consciousness	15	25.8
Vomiting	10	17.2
Motor deficit	7	12.1
High blood pressure	6	10.3
Complex partial crisis	3	5.1
Nausea	3	5.1
Stiff neck	3	5.1
Ataxia	3	5.1
Nystagmus	3	5.1
Behavioural disorders	2	3.4
CT Results		
Intraparenchymatous bleeding	30	51.7
Possible AVM presence	16	27.5
Subarachnoid bleeding	11	18.9
Brain stroke	1	1.7
N = 58		
Note: Only five patients met the criteria for epilepsy, the remaining patients with seizures had acute symptomatic seizures.		

Table 2 **Angiographic characteristics of embolized arteriovenous malformations.**

Angiographic Characteristics	Number	Percentage
AVM Localization		
Parietal	21	36.2
Temporal	15	25.8
Occipital	7	12.1
Frontal	6	10.3
Cerebellar	4	6.8
Parietal-occipital	3	5.1
Frontal-parietal	1	1.7
Interhemispheric	1	1.7
Associated Aneurysms		
Yes	4	6.8
Spetzler and Martin AVM Classification		
Grade II	7	12.1
Grade III	34	58.6
Grade IV	13	22.4
Grade V	4	6.8
<i>N = 58</i>		

During the second embolization session, a patient with a left parietal AVM, grade III according to the Spetzler and Martin classification, with a catheterized arterial pedicle belonging to the angular artery, developed Gerstmann's syndrome after the superselective test, which provokes finger agnosia, right-left confusion, dyscalculia and dysgraphia. Therefore, it was decided to catheterize the other arterial pedicle to perform the embolization test. There was also a patient with grade II monopedicular malformation (Figure 1) located in the motor cortex and the afferent pedicle of the middle cerebral artery who presented a distal brachial monoparesis. Despite the test's positive results, it was decided to perform the embolization, taking into account the risk-benefit ratio, evaluated as favorable. Since this was a young male patient with a history of bleeding and a high risk of rebleeding, he was immediately removed from the study with a distal brachial paresis, from which he subsequently recovered with physiotherapy. Likewise, there was a patient with a grade III left frontal-parietal AVM who presented a positive test result in her third embolization session. In view of that, having also evaluated the risk-benefit ratio as favorable, the decision was taken to embolize the pedicle malformation, pro-

ducing a mild neurological deficit, from which the patient fully recovered through physiotherapy one week after embolization. It is significant that 99.2% of patients with a negative propofol superselective test result did not develop post-embolization neurological deficits, and only one of the patients with a negative superselective test result developed slight contralateral fasciobrachial paresis three days after embolization. In this case a spontaneous recovery was observed and no evidence of infarction was found on CT scan. This deficit was attributed to an inflammatory process following the administration of Histoacryl.

Bearing in mind a risk-benefit ratio evaluated as favorable, six out of ten patients with positive propofol test results were embolized. Five of them presented neurological deficits similar to those observed during performance of the test, and only one did not show any neurological deficit. A CT scan was performed 72 hours after the procedure in all patients with a positive test result who were treated. The case of one patient with a positive test result who was treated and developed a focal neurological deficit is shown in Figure 2.

Table 3 shows the percentage of arterial pedicles with positive or negative propofol test

Figure 1 Patient with stage II monopedicular Spetzler and Martin AVM with positive propofol test. A) Right frontal view of an internal carotid diagnostic angiogram. B) Superselective catheterization of the malformation nidus. C) Post-embolization angiographic control.

results and the post-embolization results. Considering the positive (neurological deficit) and negative results of the superselective test with propofol, and taking the onset of neurological deficit after embolization as the “golden rule,” the sensitivity, specificity, PPV and NPV were calculated.

The test’s sensitivity, defined as its ability to determine the presence of brain eloquence, was 83.3%, meaning that it has an 83.3% probability of being positive if the explored area is eloquent. The test’s specificity, defined as its ability to detect the absence of brain eloquence in a non-eloquent area, was 99.2%. Thus, the test’s probability of presenting a negative result is 99.2%. These results confirm the test’s high efficacy for determining eloquent brain areas during AVM embolization. In other words, the proportion of eloquent brain areas in patients with a positive test result was 83.3%, and the proportion of non-eloquent areas in patients with a negative test result was 99.2%; that is, PPV and

NPV were 83.3% and 99.2%, respectively. Finally, there were no adverse reactions to propofol despite the use of 20 mg doses, reaching 40 mg in patients with positive results when it was decided to catheterize another arterial pedicle. Twenty or 40 mg doses were also used in patients with negative results in whom the microcatheter changed its position.

Discussion

The superselective test is an essential tool for endovascular treatment of intracranial and extracranial lesions. The endovascular treatment of AVMs is carried out to avoid the embolization of angiographically occult vessels supplying the normal brain tissue. These vessels cannot be observed during superselective angiography performed before embolization, due to the high flow within the nidus (sump effect), and can subsequently be occluded due to changes in he-

Figure 2 Patient with stage III AVM with positive propofol test and neurological deficit post-embolization. A,B) Frontal and lateral views of the first diagnostic angiogram show arterial feeders coming from the SCA. C,D) Frontal and lateral views of the post-embolization angiogram show complete obliteration of the AVM and n-BCA. E,F) 72 h post-intervention CT image shows n-BCA and a cerebellar infarction.

Table 3 Percentage of superselective tests with propofol and presence or absence of neurological deficit after embolization.

Propofol test (128)	Embolization Sessions (91)		
	Postembolization neurological deficit in patients undergoing a propofol test		
	Yes	No	Total
Positive 10 (7.8%)	5 (TP)	1 (FP)	6
Negative 118 (92.2 %)	1 (FN)	117 (TN)	118
Total	6	118	124

Note: 91 embolization sessions and 128 propofol tests were performed out of which 10 were positive, 6 were embolized; the remainder were catheterized in another arterial pedicle and, after verifying the negative result of the test, were embolized. Sensitivity, specificity, positive and negative predictive values were calculated.

TP: true positives FP: false positives FN: false negatives TN: true negatives.

modynamic conditions, resulting in a stroke. Several authors have reported that superselective tests can identify situations where embolization causes neurological deficit, but these are relatively minor^{15,27-30}.

The value of a superselective test is strongly debated. Opponents claim that if the contrast medium does not flow into the normal vessels during superselective angiography due to the summation effect, the provocative agent will not flow, producing a false negative result. They claim that the hemodynamic changes occurring during embolization are not simulated during the test and the potential effect of proximal reflux during embolization cannot be evaluated. Furthermore, they prescribe general anesthesia to perform the neurological evaluation, lest the patient's movements during critical moments jeopardize the procedure. They conclude that a careful assessment of AVM anatomy (angio-architecture and location with respect to the brain's eloquent areas) and the use of intranidal positions for the microcatheter in embolization may be safer than the superselective test to prevent ischemic complications^{5,31,32}.

However, supporters of the superselective test maintain that it complements vascular anatomy analysis minimizing ischemic complications, and many believe that general anesthesia is not essential to perform the embolization test safely^{5,17}. The results of this study show the test's high specificity and sensitivity for identifying eloquent areas of the brain.

Generally speaking, amobarbital is a short-action barbiturate that primarily affects the gray matter by inhibiting postsynaptic neurons in deep and cortical gray matter, as well as in the hippocampus, through the gamma acid receptor - aminobutyric A (GABA A), with no significant effect on the white matter. This barbiturate has usually been used to perform the test¹⁷.

Nevertheless, due to the current difficulties regarding amobarbital availability and interruptions in its supply, some institutions have assessed available anesthetics with quick onset, short duration, low incidence of adverse effects and similar safety profiles. Recent reports support the idea of performing the provocation test with lidocaine or in combination with other substances. Lidocaine inhibits the gray and white matter, blocking voltage-dependent sodium channels. It has also been claimed that it would be able to disclose deficits not detected by the sole use of amobarbital¹⁵.

The use of etomidate^{18,20}, methohexital^{18,19} and propofol²¹⁻²⁶ has also been suggested as alternative anesthetics to temporarily suspend one cerebral hemisphere's function. Etomidate was considered a viable alternative to amobarbital. Nevertheless, a study³³ drew attention to the risk of adrenal insufficiency, reversible through cortisone administration in critically ill patients requiring ventilation. Buchtel et al.¹⁹ stated that sodium methohexital (Brevital) may be equivalent to amobarbital. However, the incidence of adverse effects has not been described and an inadequate product supply has been reported. Some studies provide information on the use of propofol in performing the Wada test²¹⁻²⁶ and, recently, in performing the superselective Wada test, with results similar to those of amobarbital^{27,28}. Propofol is a non-toxic anesthetic for the vascular endothelium³⁴ that crosses the blood-brain barrier and acts on the central nervous system (CNS).

Propofol (2,6 di-isopropylphenol) is insoluble in water. Its solution is stable at pH values in the 7.0-8.5 range²¹, and its effect may be mediated by the inhibition of N-methyl D-aspartate receptors, which modulate the calcium influx pre-synaptically or by direct activation and postsynaptic potentiation through the CNS's GABA A

and the chloride channels of glycine receptors³⁵. The reported side-effects of propofol's use are cardiopulmonary dysfunction and epileptic seizures during intravenous injection and vascular pain and transitory hyperesthesia during accidental intra-arterial injection²¹⁻²³. The other reported side-effects are related to intra-carotid administration while performing the Wada test. Mikuni et al.²² evaluated the clinical symptoms following propofol administration and grouped them under three categories of side-effects: grade I: eye pain, facial contortion, lacrimation, laughing, apathy; grade II: confusion, head and eye version, and grade III: increased muscle tone with twitching and rhythmic movements or tonic posture. Symptoms in grades I and II are also reported as potential adverse effects of amobarbital^{17,23,36}. Eye pain, facial contortion, and lacrimation are caused by the anastomosis of peripheral vessels or crossovers between the internal and external carotid systems. Laughing and apathy are typically psychological effects of the anesthetic. Confusion, involuntary movements and head and eye version movements may reflect the loss of inhibition of the injected side in the frontal lobe²³. Stage III symptoms after amobarbital administration are relatively rare^{21,22}. Other reports indicate that propofol is a less sedative drug allowing rapid recovery and showing no residual sedative effect, even after repeated injections²³. In a comparative study between propofol and amobarbital²³, severe adverse reactions occurred less frequently than in the series reported by Mikuni et al.²². Risk factors for the occurrence of relatively severe side-effects were age (more than 55 years old), a total dose of propofol higher than 20 mg and a second injection over 10 mg. This contrasts with a comparative study of amobarbital and propofol²³ where none of the 19 patients receiving a second dose (ten of whom received a second propofol dose on both sides) had an adverse reaction. Another propofol complication is the "propofol infusion syndrome" consisting of acute refractory bradycardia and asystole. This syndrome may be caused by direct inhibition of the respiratory chain or by impairment of the propofol-mediated mito-

chondrial metabolism of fatty acids³⁷. For this reason, the authors of this report do not recommend the use of propofol in patients with mitochondrial diseases. Mikati et al.²³ consider that as indicated by other authors^{21,22,24,25}, propofol is a reasonable alternative to the use of amobarbital as an anesthetic to perform the Wada test. Feliciano et al.²⁸ found no adverse effects of the superselective test with a 7 mg propofol dose.

The absence of adverse effects in our series, despite the use of 20 mg doses, higher than those reported in the literature, even with reinjection during the same embolization session, can be explained by the superselective administration, which prevents the peripheral cholinergic effects of propofol occurring in intra-carotid administration. In the present series, the superselective test with propofol showed high sensitivity and specificity, 83.3% and 99.2% respectively, and PPV and NPV of 83.3% and 99.2%, respectively, with a total absence of adverse effects. Its proven efficacy and safety together with the high availability and low cost of the substance validate the propofol superselective test in identifying eloquent brain areas during AVM embolization. This test is a useful and essential tool that increases the safety of the procedure, and may help to reduce ischemic complications after embolization, or at least predict them accurately. Nonetheless, these results should be carefully evaluated, given the small size of this series and the fact that out of the total number of patients with positive results, only six have been embolized.

Conclusions

Propofol is a widely available inexpensive agent with an adequate safety profile. It has a low incidence of adverse effects when administered by intranidal injection to perform the superselective test, a procedure applied before AVM embolization for predicting the occurrence of post-embolization ischemic complications. In this study, propofol proved to be a safe and effective alternative to amobarbital.

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