Case series

Selective arterial temporary flow arrest with balloons during transvenous embolization for the treatment of brain arteriovenous malformations: a feasibility study with MRI-monitored adverse events

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ABSTRACT

Background The technique of endovascular transvenous embolization for brain arteriovenous malformations (AVMs) has emerged in the last 8 years as a very promising therapeutic alternative for otherwise incurable cases. Selective temporary flow arrest during transvenous endovascular embolization (TFATVE) is a novel adaptation of our previously described transvenous approach, which employs hyper-compliant balloons intra-arterially for the selective occlusion of arterial feeders during ethylene vinyl copolymer (EVOH) injection, in order to reduce intra-nidal pressure and increase nidus occlusion rates.

Methods We performed a feasibility study of the TFATVE technique between January 2016 and April 2020. Consecutive patients were included. All patients had at least one axial brain MRI or CT in the first 48 hours following intervention, and at least one brain MRI scan within the first postoperative month, in order to detect both silent and clinically evident adverse events. Patients’ demographics, angio-architectural characteristics, total injection and procedure times, angiographic and clinical outcomes were analyzed.

Results 22 patients underwent TFATVE during transvenous endovascular treatment of brain AVMs. Among them, 86.4% were high Spetzler-Martin’s grade. Good clinical outcome (modified Rankin Scale <2) was achieved in 95.5% of the cases, with 0% of procedure-related mortality and 4.5% of clinically significant, procedure-related morbidity. Total occlusion of the nidus was achieved in >90% of the cases at the end of the procedure and angiographic stability was achieved in all cases; 100% of the cases had angiographic cure at follow-up.

Conclusions TFATVE seems a safe and effective technique when conducted in carefully selected patients in highly specialized centers.

INTRODUCTION

The treatment of brain arteriovenous malformations (AVM) represents a therapeutic challenge, regardless of the chosen modality. Nevertheless, for ruptured lesions, there is a clear clinical benefit1-3 of invasive treatments. With a reported yearly risk of 6–18%4-6 and up to 34.4% per annum for ruptured lesions with exclusively deep venous drainage,7 AVM rupture is retained as the most important factor of disability and mortality.8

Although necessary, invasive treatment for AVMs with deep or eloquent localizations remains problematic in many cases, with high complication rates and moderate technical outcomes for neurosurgical techniques.9-11 The endovascular transvenous approach has emerged as a very promising therapeutic alternative for technically challenging and/or otherwise incurable brain AVMs.12 The technique is particularly beneficial in order to cure small, deep niduses or residual niduses, as a final stage of treatment.12,14

The selective temporary flow arrest during transvenous endovascular embolization (TFATVE) is an adaptation our previously described transvenous embolization technique.12 This novel adaptation employs hyper-compliant balloons intra-arterially, for the selective reduction of intra-nidal pressure, allowing for the treatment of larger nidi. We aim to describe the technique and assess its safety.

METHOD

Study design and participants

This is a cohort study on consecutive patients treated with the TFATVE technique between January 1, 2016 and April 30, 2020. The institutional review board and ethics committee approved the study protocol. All subjects or legal guardians signed an informed consent form. This study was performed in accordance with the Code of Medical Ethics of the World Medical Association (Declaration of Helsinki, 2014) and reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.15

Patient selection and endovascular technique

Among 335 patients with brain AVMs, who underwent endovascular treatment at our institution during the same period, 22 patients underwent treatment with the TFATVE technique.

The patients were selected for this technique according to our previously reported criteria for transvenous endovascular embolization, such as small and residual nidus, otherwise inaccessible by endovascular or surgical means and deep location.12 The endovascular transvenous embolization has been extensively described by our group in previous
the creation of apparent diffusion coefficient (ADC) maps; gadolinium-enhanced MRIs of the transvenous embolization for AVMs has been described elsewhere.15

The balloon catheter (Eclipse, Eclipse 2L, Scepter XC, Scepter C or Hyperform) was positioned in a straight segment of the middle cerebral artery (usually M2), anterior cerebral artery (usually A2), or posterior cerebral artery (usually P2), according to the AVM anatomy and feeders. The choice of feeders for the temporary flow arrest were selected on the basis of the larger and hemodynamically dominant feeders for the nidus supply. The goal of the balloon position was to occlude the ostium of the feeder, without it being necessarily positioned inside the feeder, since the ethylene vinyl copolymer (EVOH) injections were always performed by the transvenous route, with one or dual injection; no arterial EVOH injection was performed in this cohort, thus it was not necessary to increase the risk of further, hyperselective navigation of the balloons inside the arterial feeders.

A flexible, dimethyl sulfoxide (DMSO)-compatible microcatheter was then navigated coaxially to selectively catheterize the AVM’s draining vein, as close as possible to the nidus. In order to allow a continuous injection and a faster penetration of EVOH in the nidus and minimize backflow in the vein, coils were used in the venous side for veins ≥5 mm in diameter, with low packing density, without use of glue; in cases with a vein <5 mm we tolerated a reflux of EVOH in the order of 3 cm. The arterial balloon was inflated before each transvenous injection; every 5 min the balloon was deflated, and we waited 2 min for reperfusion after inflating the balloon again. During the interventions we maintained a systematic mean arterial pressure 20 mm Hg lower than the usual for each patient, using appropriate doses of intravenous urapidil, with an electrical syringe. No further anticoagulant therapy was administered post-intervention.

Follow-up imaging
The patients underwent brain MRI performed in a 3 T system (Achieva, Philips Medical System) or, in cases of contraindication, a CT scan, at 24–28 hours post-TFATVE. A second brain MRI was performed within a month following TFATVE. Four-axis selective digital subtraction angiography (DSA) was performed at 6 months post-intervention, and, if complete occlusion was confirmed, MRI was performed at the 24-month follow-up. MRIs were evaluated by senior neuroradiologists and included systematically diffusion-weighted imaging (DWI) sequences with the creation of apparent diffusion coefficient (ADC) maps; gadolinium injections were performed, whenever deemed necessary.

Clinical follow-up
All patients had a neurological examination by a senior neuroradiologist and anesthesiologist before treatment, at awakening, at discharge, and at 6 month follow-up.

Statistical analysis
Descriptive statistical analysis was performed, using the Student t-test for quantitative data, after appropriate testing for normal distribution (de Agostino-Pearson test) and the χ² test for qualitative data. The Statistica software (StatSoft, GE) was used. The level of statistical significance was p≤0.05.

RESULTS
Patient population
Twenty-two patients—14 (63.6%) men and eight (36.4%) women, mean age 39 years (SD 16, 95% CI for the mean: 33 to 47), among them two adolescents—were treated for a brain AVM with the technique of selective TFATVE. Their initial modified Ranking Score (mRS) at admission was 0 for 13 (59.0%) patients, 1 for four (18.1%) patients, 2 for three (13.6%) patients, 4 for one (4.5%) patient, and 5 for one (4.5%) patient. Clinical presentation included intraventricular hemorrhage in seven (31.8%) patients, intracranial hematoma in six (27.3%), subarachnoid hemorrhage in one (4.5%), epilepsy in three (13.6%), stroke in one (4.5%), headache in two (9.1%) patients, and ‘other’ in two (9.1%) of the cases. Spetzler-Martin (S-M) classification was 1 for one (4.5%) case, 2 for 6/22 (27.3%), 3 for 13/22 (59.1%), 4 for one (4.5%) case, and 5 for one (4.5%) case. Nineteen out of 22 cases (86.4%) were high S-M grade (online supplemental table).

AVM characteristics
The AVMs were ruptured in 14/22 (63.6%) and unruptured in 8/22 (36.4%) of the cases. Nidi locations included eloquent areas in most of the cases (17/22 cases, 77.3%). Nidi sizes were <3 cm in 12 (54.5%) cases, 3–6 cm in nine (40.9%) case, and >6 cm in one (4.5%) case. Associated aneurysms were identified in 6/22 cases (27.3%), among which were two cases of aneurysms located at the level of Willis (9.1%) and 4/22 cases with intranidal aneurysms (18.2%). A venous pouch was present in one (4.5%) case.

The AVMs were located in the hemispheres in 14/22 (63.6) cases, the basal ganglia in three cases (13.6%), the corpus callosum in one case (4.5%), the choroid plexus in another case, and the posterior fossa in three cases (13.6%). The AVMs had exclusively deep venous drainage in 9/22 (40.9%) cases, and included, but were not limited to, deep venous drainage in 5/22 (22.7%) cases, while the remaining 8/22 (36.4%) cases had exclusively superficial venous drainage.

Technical facts
The temporary flow arrest was performed in arterial feeders of the anterior circulation in 13/22 (59.1%) cases, among which were three cases (3/22, 13.6%) with two balloons in two arterial feeders, and in the posterior circulation in 5/22 (22.7%) cases, among which was one case (1/22, 4.5%) with two balloons in two feeders. There were 4/22 (22.7 %) cases with temporary balloon occlusion in both the anterior and posterior circulations (figure 1). In cases with two balloons, these were inflated during the EVOH injections simultaneously. The EVOH injection was always transvenous and did not always correspond to dual transvenous injection.

The patients had overall one session until cure in nine (40.9%) cases, two sessions in eight (36.4%) cases, three sessions in two (9.1%) cases, and more than three sessions in three cases (13.6%). In the vast majority of the cases (20/22, 90.9%) the session with the selective, temporary flow arrest was the last session; only in two cases (9%) was the flow arrest session followed by another,
last session (by simple transvenous embolization), in order to obtain total occlusion of the nidus. The transvenous approach involved the use of loose coiling in the draining vein in 15/22 (68.2%) of the cases; for the rest of the cases (7/22, 31.8%) the transvenous injection was performed without the adjunct use of coils. One case (4.5%) was performed with dual microcatheter injection in the venous side.

The mean total injection time of the liquid embolic material by the transvenous route was 10±6 min (arithmetic mean±SD) and was delivered as a single injection in 9/22 (40.9%) cases, as two injections in 8/22 (36.4%), as three injections in 3/22 (13.6%), and as more than three injections in 2/22 (9%) cases. The time length per injection ranged from 3 to 8 min. The mean amount of liquid embolic material used per procedure was 13.5±20 mL (arithmetic mean±SD, median 9 mL). Mean total procedure time was 88 min (±SD: 44 min, 95% CI of the mean: 68 to 106 min), defined as groin puncture to closure.

Clinical outcomes
mRS scores at discharge were 0 for 11/22 (50.0%) patients, 1 for 3/22 (13.6%), 2 for 4/22 (18.2%), 3 for 3/22 (13.6%), and 4 for 1/22 (4.5%) patients. At 6 month controls, mRS was 0 for 11/22 (50.0%) patients, 1 for 6/22 (27.3%), 2 for 3/22 (13.6%), and 3 for 2/22 (9.1%) patients. Respective values at 1 year were 13/22 (59.1%), 5/22 (22.7%), 3/22 (13.6%), and 1/22 (4.5%). At 6 and 12 months 91% and 95.5% of the patients were independent in their everyday lives, respectively (table 1).

Angiographic outcomes
In all but two cases, in 20/22 (90.9%) cases at the end of the procedure there was complete occlusion of the AVM. The latest DSA follow-up was 12 months and it showed stability of the angiographic outcome for all patients. The small nidus remnant of one patient was subsequently addressed by transvenous embolization (online supplemental table).

Clinical and angiographic evolution
The overall rate of adverse events was 9% and the percentage of good clinical outcome (mRS <2) was 95.5% at 1 year post-intervention. Procedure-related and overall mortality was 0%. Overall procedure related morbidity was 9% and clinically significant procedure-related morbidity was 4.5%. Absence of delayed re-bleeding was found. Total occlusion of the nidus and angiographic stability of the result was achieved in all cases.

Axial imaging follow-up of adverse events
Eighteen patients (18/22 (82%)) had a brain MRI within 48 hours post-intervention; the remaining 4/22 were initially monitored by CT scan. All of the patients had at least one post-procedure brain MRI, either during hospitalization, or during follow-up within the first month after discharge. Absence of imaging-confirmed venous ischemia was documented for all patients, including absence of extensive vasogenic edema of the region in which the nidus was located, absence of hemorrhage of the region, and absence of thrombus inside a vein. Vasogenic edema around the cast of EVOH, without a decrease in ADC values, was found in 8/18 (44%) of the cases and had resolved on follow-up imaging.

There was one case with early-onset, clinically evident arterial ischemia (1/22, 4.5%) (infarct with low ADC values and arterial distribution), which is described below. There was one case (1/22 (4.5%)) with two clinically silent spots on the post-procedure MRI. There was no late-onset hemorrhage, or late-onset arterial or venous ischemia, detected in the axial imaging.

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Table 1  Clinical evolution of patients by means of modified Ranking-Scale score

<table>
<thead>
<tr>
<th>Pre-Tx</th>
<th>Discharge mRS (n=22)</th>
<th>6 month mRS (n=22)</th>
<th>≥12 month mRS (n=22)</th>
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<tbody>
<tr>
<td>mRS</td>
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<td>1</td>
</tr>
<tr>
<td>0</td>
<td>12</td>
<td>11</td>
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<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>11</td>
<td>3</td>
</tr>
</tbody>
</table>

Gray-shaded numbers indicate the number of patients with clinical worsening in regard to pretreatment clinical status. Light gray indicates worsening non-related to the procedure or the AVM of the patient. Pink shaded numbers indicate the number of patients with clinical improvement in regard to pretreatment clinical status.

AVM, arteriovenous malformation; mRS, modified Rankin Scale; Tx, treatment.
Complications
All cases were technically feasible. Absence of cerebral venous ischemia, early or delayed, was confirmed by imaging for all treated patients. There was one case of arterial ischemia (1/22 (4.5%)), in a patient who was treated for a right temporal AVM, S-M 3. The AVM’s feeders were the right anterior choroidal artery and right anteromedial branches of the posterior cerebral artery, and the venous drainage was by a single, exclusively deep collector to the basal vein of Rosenthal. The transvenous injection was performed with TATVE with two balloons, inflated in the right middle cerebral artery (M1 segment) and in the right posterior cerebral artery, respectively. The total EVOH injection time was 7 min 55 s and the total procedure time 48 min (grain puncture to closure).

In the immediate post-procedure period, the patient experienced left arm and leg hemiplegia and hemianesthesia and left homonymous hemianopia. The MRI showed restricted diffusion in the posterior limb of the internal capsule and perilesional vasogenic edema around the nidus. The perforators were patent and visible on the control angiogram at the end of the procedure. The symptoms partially regressed during hospitalization and further improved during follow-up. The patient, who had an mRS score of 1 before the treatment, was discharged with mRS 2 and was mRS 1 at 6 months and mRS 0 at 1 year.

In another case (1/22 (4.5%)), a small hematoma was detected in the first hours post-treatment, in a patient with a ruptured AVM, undergoing the second and last embolization session for a S-M 3, right temporal AVM. The embolization included two EVOH injections, one of 6 min 4 s and the other of 5 min 48 s. Total procedure time (grain puncture to closure) was 200 min. The patient suffered deficit of the right side, which partially regressed during hospitalization. The patient was mRS 3 and 2 at 6- and 12-month follow-up evaluations, respectively.

DISCUSSION
Deep AVMs and, until recently, inaccessible angioarchitectural types or post-treatment nidi remnants have been lately addressed by transvenous embolization, with impressively high cure rates. Within the last 5 years an increasing number of studies show that the transvenous route may be curative in otherwise inaccessible cases. The relative indications include cases with some cases. The key factor in the technique presented herein is use of a selective balloon occlusion, which allows for pressure and flow reduction/arrest without temporarily occluding the vein before the nidi. We only experienced one case (4.5%) of a small hematoma detected in the first hours post-treatment in a patient with a ruptured AVM.

Since selective balloon inflation remains an additional invasive element during the procedure, we sought to assess the additional risk objectively and to correlate it with the benefit of this novel approach. For this reason we were the first team to monitor all cases and adverse events, even silent ones, by MRI. Our findings confirmed absence of neither early nor delayed venous ischemia. Silent arterial ischemic spots were found in one case (4.5%) and clinically evident arterial ischemic in another (4.5%).

Even though the concept of selective flow arrest is novel, systemic cardiac arrest and hypotension have been already attempted, aiming at better control of the liquid embolic agent clinical and angiographic results are in agreement with these experimental findings.
and better results. Nevertheless, the risks of complications from these techniques are not negligible.\textsuperscript{23, 24} Multiple periods of cardiac arrest and hypotension have the potential to produce cardiac and neurologic injury.\textsuperscript{25} Bendok et al and Lee et al described cardiac complications from adenosine use, such as increased troponin, ventricular tachyrhythmias, atrial fibrillation and bradyarrhythmias.\textsuperscript{26, 27} Al-Mousa et al point out that there are several case reports of bronchospasm after adenosine administration.\textsuperscript{25}

In a recent publication by Waqas et al, flow control was attempted in 12 cases, using concurrent transient rapid ventricular pacing or intravenous adenosine and temporary occlusion of arterial feeders by balloon inflation, while employing retrograde, obstructive coiling and N-butyl cyanoacrylate (NBCA) injection of the vein, with subsequent EVOH injection transvenously in retrograde fashion. In this study the authors attempted to exploit a complete flow arrest–total flow control, by simultaneous pharmacological and mechanical means, transiently occluding the arterial pedicles and permanently occluding the draining vein. They reported 20\% of intraprocedural hemorrhagic complications.\textsuperscript{28}

While in our series there are similar inclusion criteria, our technique is less aggressive, without systemic pharmacological cardiac arrest, neither total inflow nor outflow flow arrest. The loose coiling used in some cases in the vein was destined to reduce the rapid outflow, and did not have a goal of occluding the veins. We relied solely on a selective flow arrest, which to our experience was enough for the occlusion of the selected nidi, with fewer intraprocedural complications.

As opposed to other techniques employing transvenous embolizations, we neither aimed for complete venous occlusion in the initial stages of the treatment, nor for transarterial injections through the balloon. We aimed to selectively reduce the inflow and pressure in the nidi, with the least invasive way possible, giving a further boost to our standard transvenous embolization technique, without additional risk coming from more aggressive approaches.

With hemorrhagic clinical presentation in 63.6\% of our cases and high S-M scores in 86.4\% of them, we believe that with 0\% mortality and 4.5\% clinically significant complications in our series the technique seems promising, given the reported complication rates in the range of 20\% for these types of lesions.\textsuperscript{29} Good clinical outcome (mRS <2) was found in 95.5\% of the patients in our series, 6 months after intervention, with an initial total occlusion rate of over 90\% and a total occlusion rate of 100\% at follow-up.

LIMITATIONS
Since this is a small series of a new endovascular technique, the sample is limited and the statistical analysis results have limited value. Nevertheless, they may depict directions for further analysis and attention with larger databases in the future.

CONCLUSION
The selective temporary flow arrest during transvenous embolization seems a safe and effective technique, especially for high-grade AVMs which have been previously treated. It should be employed in carefully selected patients and in highly specialized centers. Further research with larger series and case-controlled studies are required to validate these findings.

Contributors Conception and design of study: CI and CM. Acquisition of data: JAAF, CEG and ANR. Analysis and/or interpretation of data: CI, CM, AR, SS. Drafting the manuscript: CI, JAAF. Revising the manuscript critically for important intellectual content: CI, CM. Approval of the version of the manuscript to be published: CI, CM, AR, SS, JAAF, ANR and CEG.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

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New devices and techniques


