Angiographic predictors of spontaneous obliteration of transarterial partially embolized brain arteriovenous malformations

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Abstract
Background: Spontaneous obliteration of cerebral arteriovenous malformations is uncommon but could occur after partial embolization.
Methods: A retrospective study of 140 patients that underwent embolization for cerebral AVMs from 2005 to August 2019 using liquid embolic agents. The angiographic outcome of patients was classified as regard complete embolization, partial embolization, and complete obliteration after partial embolization. The parameters studied included size, location, number of arterial feeders, number of draining veins, rupture status, embolic agent, and patient factors as well.
Results: The study patients included 74 (53%) females and 66 (47%) males. Their age ranged from 7 to 43 years old. One hundred and eight patients (77%) presented with hemorrhage. The AVM grades were grade II in 57 (40.7%) patients and grade III in 56 (39.3%) patients. Sixty-one (43.57%) patients were treated by n-Butyl Cyanoacrylate and 71 (50.71%) patients were treated with Onyx, and both materials were used together in 8 cases. Follow-up angiography was done from 6 to 36 months after embolization. The rate of complete occlusion in all patients was 61.43% (86 patients). There were three groups of patients, the first group had complete occlusion of the nidus at the time of embolization and included 68 (48.57%) patients. The second group had partial embolization with partial occlusion of the nidus 54 patients (38.57%). The 3rd group included 18 patients (12.85%) with complete nidal occlusion on follow up after partial embolization. The delay in the venous drainage of the AVM to the late arterial phase or early venous phase with flow stasis was a significant predictor of future obliteration on follow up after partial embolization. Other significant parameters that were associated with the progressive disappearance of the AVM nidus on follow up after partial embolization are presentation with hemorrhage, AVMs size less than 3 cm, the presence of single draining or double draining veins, superficial venous drainage, and one or 2 arterial feeders.
Conclusion: Spontaneous closure of intracranial arteriovenous malformations after partial embolization may be encountered in cases of stasis of flow during embolization procedure with a delay of the venous drainage. A long-term follow-up of more cases over many years is required to confirm the validity of this conclusion.

Keywords
Arteriovenous malformations, angiographic cure, partial embolization, complete obliteration, venous drainage, flow stasis

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Introduction
Pial arteriovenous malformations although rare, are a common cause of stroke in the young population. Their management carries great controversy worldwide. There is no consensus on the optimum treatment. Microsurgery plays a major role in the immediate eradication with a good result in low-grade lesions, but it carries a high rate of morbidity in the high-grade ones. Radiosurgery can be used in many lesions with a success rate. It can be used alone or after surgery or after partial embolization. Endovascular embolization is an important tool of AVM treatment. It can be used alone or in combination with surgery and/or radiosurgery. Some centers exercise endovascular embolization as a curable minimally invasive tool with a comparable obliteration rate, low morbidity, and mortality. Partial embolization is used frequently in the literature to occlude an aneurysm or high flow fistula or part of the multisession treatment of the nidus. Some studies indicated that partial embolization may carry the risk of increased hemorrhage. Many previous studies reported the disappearance of AVM nidus

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after partial embolization or even after surgery. We experienced obliteration of the nidus after unintended partial or subtotal embolization in some of our cases of embolization. Those cases were Fortunately discovered on follow-up. The study is discussing the possible underlying factors standing behind this phenomenon.

**Methods**

A retrospective study in a consecutive series of 140 patients underwent embolization for an AVM from 2005 to August 2019 using liquid embolic agents. The occlusion of AVM after embolization was studied. Patients were categorized into 3 groups. The first group included patients with complete obliteration at the time of embolization, the second one included cases with partial obliteration after partial embolization, and the third included patients with complete obliteration after partial embolization. The parameters of the studied groups included the demographic and clinical data: (1) age, sex; (2) clinical presentation; (3) history of prior hemorrhage; and (4) Spetzler-Martin (SM) grading scale and other angioarchitecture characteristics (Tables 1 and 2). MRI and CT scans were done in all cases. CTA was done in some cases. A full assessment of the whole cerebral circulation by digital subtraction angiography was done in all cases in a separate procedure. All patients who presented with hemorrhage were embolized after the resolution of the hematoma or after evacuation.

The Femoral artery approach was used in all cases. General anesthesia with endotracheal intubation was used in all cases. A 6-F guiding catheter (Envoy; Codman, USA) or (Chapron, Microvention), to guard against blood clotting inside the guiding catheter. Continuous flushing of normal saline (0.9 NaCl) containing heparin (5000 U/500 mL saline) and 5 mg nimodipine/ 500 mL saline to prevent vasospasm. Heparin was reversed using protamine before microcatheter removal. Superselective navigation of the AVM feeders was done using flow-directed microcatheters after complete cerebral angiography. Careful analysis of the super-selective angiogram was done to assess the optimum position of the tip of the microcatheter inside the nidus, on- passage arteries, intranidal aneurysms, high flow fistulas, and vein location. Road-mapping was used during material injection in all lesions.

The embolizing agent was chosen according to the angioarchitecture of the nidus. Onyx 18 (Medtronic) was used in lesions with multiple compartments and feeders with enough length for the reflux of embolizing material. Onyx was slowly injected into the nidus under continuous roadmap fluoroscopy using the “push and plug” technique. If any reflux along the microcatheter was observed or the material reached the draining vein, the injection was stopped.

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**Table 1.** Comparison between the three studied groups according to demographic and clinical data.

| Location  | Completely obliterated (n = 68) | Partially obliterated (n = 54) | Partially embolized with complete obliteration (n = 18) | \( p_1 \) | \( p_2 \) |
|-----------|-------------------------------|-----------------------------|---------------------------------|--------|--------|
| Age (years) |                               |                             |                                 |        |        |
| 1–18      | 13 (19.1%)                    | 12 (22.2%)                  | 4 (22.2%)                       | 0.902  | FF \( p = 1.000 \) |
| >18       | 55 (80.9%)                    | 42 (77.8%)                  | 14 (77.8%)                      |        |        |
| Sex       |                               |                             |                                 |        |        |
| Male      | 33 (48.5%)                    | 26 (48.1%)                  | 7 (38.9%)                       | 0.753  | 0.495  |
| Female    | 35 (51.5%)                    | 28 (51.9%)                  | 11 (61.1%)                      |        |        |
| Presentations |                           |                             |                                 |        |        |
| Hemorrhage| 59 (86.8%)                    | 34 (63%)                    | 15 (83.3%)                      | \( MC_p = 0.022^* \) | \( MC_p = 0.251 \) |
| Fits      | 6 (8.8%)                      | 16 (29.6%)                  | 2 (11.1%)                       |        |        |
| Headache & others |                        | 4 (7.4%)                    | 1 (5.6%)                        |        |        |
| Location  |                               |                             |                                 |        |        |
| Frontal   | 9 (13.2%)                     | 12 (22.2%)                  | 3 (13.7%)                       | \( MC_p = 0.285 \) | \( MC_p = 0.800 \) |
| Parietal  | 18 (26.6%)                    | 14 (25.9%)                  | 7 (38.9%)                       |        |        |
| Temporal  | 6 (8.8%)                      | 8 (14.8%)                   | 4 (22.2%)                       |        |        |
| Occipital | 21 (30.9%)                    | 7 (13%)                     | 3 (16.7%)                       |        |        |
| IV        | 4 (5.9%)                      | 2 (3.7%)                    | 0 (0%)                          |        |        |
| BG        | 1 (1.5%)                      | 0 (0%)                      | 0 (0%)                          |        |        |
| Callosal  | 3 (4.4%)                      | 1 (1.9%)                    | 0 (0%)                          |        |        |
| TH        | 1 (1.5%)                      | 4 (7.4%)                    | 1 (5.6%)                        |        |        |
| BS        | 2 (2.9%)                      | 0 (0%)                      | 0 (0%)                          |        |        |
| CBLR      | 3 (4.4%)                      | 6 (11.1%)                   | 0 (0%)                          |        |        |

FE: Fisher Exact; MC: Monte Carlo; \( p_1 \): \( p \) value for comparing between the three studied groups; \( p_2 \): \( p \) value for comparing between Incomplete and Partial complete.

*Statistically significant at \( p \leq 0.05 \).
stopped for 1–2 min and then resumed to redirect Onyx to different parts of the lesion. Control angiographies were done regularly during Onyx injection to assess the nidus filling and the venous drainage. A DMSO-compatible delivery microcatheter was used including Marathon (Medtronic), Apollo (Medtronic), or Sonic (Balt, France). Microwires included Mirage (Medtronic) and hybrid (Balt).

N-Butyl Cyanoacrylate (NBCA) (Trufill; Cordis, Miami Lakes, FL) was used in direct high flow fistula and feeders with no safe distance for the reflux of the embolizing agent. The concentration of the NBCA-Lipiodol® (Guerbet, France) mixture was determined after superselective angiography to assess the flow. Low concentration (about 20%) was chosen for most cases but high concentrations (about 75%) were chosen for high-flow fistulas. The microcatheters were flushed with a 25% dextrose solution and then the NBCA-Lipiodol mixture was infused under roadmap fluoroscopy. No reflux was permitted during the NBCA injection. Rapid

Table 2. Comparison between the groups according to imaging criteria.

| Spetzler–Martin grade | Completely obliterated (n = 68) | Partially obliterated (n = 54) | Partially embolized with complete obliteration (n = 18) | p1 | p2 |
|-----------------------|--------------------------------|-------------------------------|------------------------------------------------------|----|----|
| I                     | 5 (7.4%)                      | 1 (1.9%)                      | 3 (16.7%)                                            |    |    |
| II                    | 36 (52.9%)                    | 15 (27.8%)                    | 6 (33.3%)                                            |    |    |
| III                   | 22 (32.4%)                    | 26 (48.1%)                    | 7 (38.9%)                                            |    |    |
| IV                    | 5 (7.4%)                      | 10 (18.5%)                    | 2 (11.1%)                                            |    |    |
| V                     | 0                              | 2 (3.7%)                      | 0 (0%)                                               |    |    |

Number of feeders

| Number of feeders | Absolutely obliterated | Partially obliterated | Partially embolized with complete obliteration | p1 | p2 |
|-------------------|------------------------|-----------------------|------------------------------------------------|----|----|
| 1 feeder          | 21 (30.9%)             | 0 (0%)                | 2 (11.1%)                                        |    |    |
| 2 feeders         | 18 (26.5%)             | 6 (11.1%)             | 6 (33.3%)                                        |    |    |
| 3 feeders         | 12 (17.6%)             | 10 (18.5%)            | 7 (38.9%)                                        |    |    |
| 4 feeders         | 5 (7.4%)               | 8 (14.8%)             | 1 (5.6%)                                         |    |    |
| 5 or more feeders | 12 (17.6%)             | 30 (55.6%)            | 2 (11.1%)                                        |    |    |

Type of venous drainage

| Type of venous drainage | Absolutely obliterated | Partially obliterated | Partially embolized with complete obliteration | p1 | p2 |
|-------------------------|------------------------|-----------------------|------------------------------------------------|----|----|
| Deep (D)                | 13 (19.1%)             | 11 (20.4%)            | 4 (22.2%)                                        |    |    |
| Superficial (S)         | 31 (45.6%)             | 19 (35.2%)            | 10 (55.6%)                                       |    |    |
| Both (SD)               | 24 (35.3%)             | 24 (44.4%)            | 4 (22.2%)                                        |    |    |

Number of veins

| Number of veins | Absolutely obliterated | Partially obliterated | Partially embolized with complete obliteration | p1 | p2 |
|-----------------|------------------------|-----------------------|------------------------------------------------|----|----|
| One vein        | 34 (50%)               | 15 (27.8%)            | 12 (66.7%)                                       |    |    |
| Two veins       | 25 (36.8%)             | 13 (24.1%)            | 4 (22.2%)                                        |    |    |
| Three or more veins | 9 (13.2%)             | 26 (48.1%)            | 2 (11.1%)                                        |    |    |

AVM size (cm)

| AVM size (cm) | Absolutely obliterated | Partially obliterated | Partially embolized with complete obliteration | p1 | p2 |
|---------------|------------------------|-----------------------|------------------------------------------------|----|----|
| <3            | 50 (73.5%)             | 21 (38.9%)            | 16 (88.9%)                                       |    |    |
| 3–6           | 18 (26.5%)             | 29 (53.7%)            | 2 (11.1%)                                        |    |    |
| >6            | 0 (0%)                 | 4 (7.4%)              | 0 (0%)                                           |    |    |

Material used

| Material used | Absolutely obliterated | Partially obliterated | Partially embolized with complete obliteration | p1 | p2 |
|---------------|------------------------|-----------------------|------------------------------------------------|----|----|
| NBCA          | 32 (47.1%)             | 20 (37%)              | 9 (50%)                                         |    |    |
| Onyx          | 33 (48.5%)             | 29 (53.7%)            | 9 (50%)                                         |    |    |
| Both          | 3 (4.4%)               | 5 (9.3%)              | 0 (0%)                                          |    |    |

No of sessions

| No of sessions | Absolutely obliterated | Partially obliterated | Partially embolized with complete obliteration | p1 | p2 |
|---------------|------------------------|-----------------------|------------------------------------------------|----|----|
| 1             | 62 (91.2%)             | 32 (59.3%)            | 16 (88.9%)                                       |    |    |
| 2             | 4 (5.9%)               | 11 (20.4%)            | 1 (5.6%)                                         |    |    |
| ≥3            | 2 (2.9%)               | 11 (20.4%)            | 1 (5.6%)                                         |    |    |

Complications

| Complications        | Absolutely obliterated | Partially obliterated | Partially embolized with complete obliteration | p1 | p2 |
|----------------------|------------------------|-----------------------|------------------------------------------------|----|----|
| Transient deficit    | 3 (4.4%)               | 3 (5.6%)              | 1 (5.6%)                                        |    |    |
| Permanent            | 2 (2.9%)               | 0 (0%)                | 0 (0%)                                          |    |    |
| Intraoperative rupture| 5 (7.4%)               | 2 (3.7%)              | 1 (5.6%)                                        |    |    |
| Alopecia             | 4 (5.8%)               | 2 (3.7%)              | 1 (5.6%)                                        |    |    |
| Catheter entrapment  | 3 (4.4%)               | 2 (3.7%)              | 0 (0%)                                          |    |    |

Status of venous drainage after EVE

| Status of venous drainage after EVE | Absolutely obliterated | Partially obliterated | Partially embolized with complete obliteration | p1 | p2 |
|------------------------------------|------------------------|-----------------------|------------------------------------------------|----|----|
| Early arterial drainage            | 0 (0%)                 | 29 (53.7%)            | 2 (11.1%)                                       |    |    |
| Late arterial drainage             | 0 (0%)                 | 20 (37%)              | 16 (88.9%)                                       |    |    |
| Mid arterial drainage              | 0 (0%)                 | 5 (9.3%)              | 0 (0%)                                          |    |    |
| Venous phase drainage              | 68 (100%)              | 0 (0%)                | 2 (11.1%)                                       |    |    |

FE: Fisher Exact; MC: Monte Carlo; p1: p value for comparing between the three studied groups; p2: p value for comparing between Partially obliterated and Partially embolized with complete obliteration.

*Statistically significant at p ≤ 0.05.
microcatheter withdrawal was done to prevent trapping of the microcatheter. All patients were monitored in the intensive care unit after the procedure for 24 to 48 h with maintaining mean arterial pressures between 65- and 75-mm Hg to prevent abrupt elevations in systolic blood pressure to reduce the risk of postembolization hemorrhage.

The number of veins, the embolic material used, and the percentage of nidal obliteration were registered as well as any complications related to the embolization procedure. Also, the phase in which the draining vein was observed at the end of the embolization session. The early arterial phase is in which we can see the major arterial branches. Mid arterial is the capillary phase. Late arterial is at the end of the capillary phase and the start of the venous phase. Clinical and radiologic follow-up was done for all patients from 6 to 36 months.

**Statistical analysis of the data**

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov was used to verify the normality of distribution of variables. Comparisons between groups for categorical variables were assessed using the Chi-square test (Fisher’s Exact or Monte Carlo correction). The significance of the obtained results was judged at the 5% level. The univariate and multivariate analyses were then performed with these same tests to assess the factors associated with significant effect on the outcome.

**Results**

This retrospective study included 140 patients diagnosed with brain AVMs since 2005 in our center. The whole patient cohort included 74 (53%) females and 66 (47%) males. Their age ranged from 7 to 43 years old with about one-third of patients less than 18 years. One hundred and eight patients (77%) presented with hemorrhage. The AVM Spetzler-Martin grading showed grade II in 57 (40.7%) patients and grade III in 56 (39.3%) patients. Sixty-one (43.57%) patients were treated with n-Butyl Cyanoacrylate and 71 (50.71%) patients were treated with Onyx, and both materials were used together in 8 cases. The rate of complete occlusion in all patients was 61.43% (86 patients). There were three groups of patients, the first group had complete occlusion of the nids at the time of embolization and included 68 (48.57%) patients. The second group had partial embolization with partial occlusion of the nids 54 (38.57%) patients. The 3rd group included 18 (12.85%) patients with complete nidal occlusion on follow-up after being partially embolized.

We compared the two groups of partially embolized cases as regards the angiographic observations that were associated with the progressive disappearance of the AVM nids on follow-up. These observations included the presentation with hemorrhage (15 patients 83.3%, \( p < 0.05 \)) (Table 1), AVMs size less than 3 cm (16 patients 88.9%), the presence of single draining vein (12 patients 66.7%), superficial venous drainage (10 patients 55.6%) and 1–3 arterial feeders (15 patients 83.3%). We observed that flow stasis and venous drainage delay to the late arterial phase or early venous phase was a significant predictor of late AVM obliteration (Tables 2 and 3) (Figures 1–3).

The encountered complications included 6 cases of intraoperative rupture resulted in 4 cases of SAH and 2 cases of parenchymal hemorrhage that required evacuation. Also, there were 5 cases of microcatheter trapping. The resulting morbidity included 7 cases with transient deficits and 2 cases of permanent neurological deficits.

| Table 3. Univariate and Multivariate logistic regression analysis for the parameters affecting partially embolized with complete obliteration \((n = 18 \text{ vs. } 122)\). |
|---------------------------------|-----------------|-----------------|
|                                 | Univariate      | Multivariate    |
|                                 | \( p \)          | OR (95% CI)     | \( p \)          | OR (95% CI)     |
| Spetzler martin grade           | 0.345           | 0.745 (0.405−1.372) | 0.801           | 1.167 (0.352−3.864) |
| Type of venous drainage         |                 |                 | 0.248           | 1.800 (0.664−4.879) |
| Deep (D)                        | 0.169           | 0.440 (0.137−1.418) |
| Superficial (S)                 | 0.126           | 0.661 (0.390−1.123) |
| Both (SD)                       | 0.026*          | 0.174 (0.038−0.790) | 0.002*          | 0.087 (0.018−0.419) |
| AVM size (cm)/≥3               |                 |                 |                 |                 |
| Material used                   |                 |                 |                 |                 |
| NBCA                             | 0.557           | 1.346 (0.500−3.627) |
| Onyx                            | 0.948           | 0.968 (0.360−2.604) |
| Both                            | 0.999           | -               |
| No of sessions/≥2               | 0.266           | 0.420 (0.091−1.937) |
| Venous phase drainage           | 0.003*          | 0.099 (0.022−0.451) | <0.001*         | 0.058 (0.012−0.273) |

OR: Odd’s ratio; CI: Confidence interval; LL: Lower limit; UL: Upper Limit.
*All variables with \( p < 0.05 \) was included in the multivariate.
*Statistically significant at \( p \leq 0.05 \).
The transient deficits included upper limb monoparesis in 3 cases improved in two weeks, transient hemiparesis in 2 cases, transient hemiparathesia in a thalamic AVM patient, and transient loss of consciousness in a thalamic AVM patient. The permanent deficit was hemiplegia in one patient due to intraoperative rupture. Another patient had pre-embolization weakness from intracerebral hematoma, the weakness increased after embolization and improved partially (grade 4 weakness) (Table 2). No procedure-related mortality occurred.

Discussion

Endovascular embolization is a minimally invasive tool to obliterate the AVM nidus aiming for nidus complete exclusion from brain circulation. Large Multi-compartmental AVM may require more than a session of embolization to decrease the incidence of hemodynamic changes of large lesions occlusion.3 “The time to stop?” during difficult AVM embolization is a critical question that came to the mind of very Endovascular interventionist, probably

Figure 1. A 33 years patient presented with IVH and hydrocephalus (a) plain CT scan axial showing IVH, (b) LT vertebral artery (VA) angiography showing Rt the AVM supplied by RT PCA branches(straight arrow), (c) LT ICA angiography showing the AVM supplied by anterior choroidal branches(straight arrow) (d) superselective angiography for the second NBCA injection(straight arrow), (e) Lt VA angiography showing nidus remnant (curved arrow), (f) axial T2 MRI follow showing nidus disappeared and normal ventricular size (g & h) late RT VA angiography showing nidus disappeared I late RT ICA angiography showing nidus disappeared.
venous outlet slowing of the AVM compartment could be the answer.

Total nidal occlusion with angiographic disappearance of the feeders and veins during angiographic follow of 18 patients after partial embolization was observed in this study. During the embolization procedure, venous drainage delay and flow stasis after the arterial phase was observed and the infusion of the embolic agent was associated with more reflux. The procedure was stopped, and all patients were scheduled for follow-up. The eighteen patients had their AVM obliterated in follow-up angiography after 6 to 36 months. The whole structure of the nidus disappeared. Feeders and drainers disappeared and normal angioarchitecture was observed in the region of the nidus.

The radiological features that were shared in most of these cases that may explain this phenomenon included a presentation with hemorrhage, AVMs size less than 3 cm, the presence of single draining or double draining veins, superficial venous drainage, and one or 2 arterial feeders. The stasis of flow and delay of venous drainage in our series is the best significant predictor that allows further thrombosis and closure of the nidus. Most of the venous drainage in spontaneously obliterated cases was

Figure 2. A twenty-seven years old patient presented with ICH (a & b) LT ICA angiography showing Lt frontal AVM supplied by ACA & MCA branches (straight arrow), (d & e) left ICA angiography (lateral and anteroposterior views) showing nidus remnant (curved arrow) (c) left ICA angiography (lateral view) showing nidus remnant (curved arrow) in late arterial phase, (f) plain radiograph showing the onyx cast in lateral view (g, h, i) late LT ICA angiography after one year showing nidus disappeared (feeders are regressed in size the arrowheads point to the feeders in (a, d, & g).
a superficial one. Also, most lesions were small (about 89% were less than 3 cm). Also, a low number of arterial feeders (one or two) was a significant predictor.

Several factors in the literature were discussed as the triggering mechanism for the AVM obliteration with or without intervention. The presentation with hemorrhage either parenchymal or SAH may result in thrombosis of AVMs either through compression or vasospasm of the feeders. Atherosclerosis and narrowing of the blood vessels of the nidus is a proposed factor. The presence of single draining or stenotic vein may allow thrombosis and disappearance of the nidus. Stasis and turbulence of the flow inside the nidus and draining vein may play a major role in thrombosis and obliteration. Also, the thrombogenic effect of the embolizing agent is another factor. NBCA is known to have a vascular inflammatory effect that may help thrombosis inside the AVM nidus. Partial embolization may decrease the angiogenic factors affecting the endothelial cells followed by a reduction in size and obliteration. Mangiafico et al. reported one case with partial embolization that progressed to angiographic obliteration and they observed a reduction of the flow to the mid arterial phase. Cellerini et al. reported 4 cases and they observed flow reduction after partial embolization. Ahmad et al. reported one case occluded after 70% occlusion of the nidus in 2 sessions. Kocur et al. and Torrico et al. each reported 2 cases after being embolized with onyx. Viñuela et al. reported 2 cases after the use Isobutyl-2-Cyanoacrylate. Also, Nas et al. reported one case with partial embolization progressed to complete obliteration. Miyachi et al. studied changes in the drainage system after embolization and concluded that stasis in the venous outflow leads to progressive AVM thrombosis and obliteration.

The achievement of complete nidal obliteration with embolization may require more microcatheter navigation or excessive infusion of the embolic agent which may be risky. Also, this may necessitate changing the decision by doing transvenous embolization or doing radiosurgery or microsurgery. So venous drainage delay may be an indication to stop the procedure, especially with the reflux of the embolic material to a dangerous point. Follow-up angiography can be done later with the possibility of an AVM cure. But the long-term follow-up is needed to ensure stable occlusion.

**Conclusion**

Spontaneous closure of intracranial arteriovenous malformations after partial embolization may occur in cases of stasis of flow during embolization procedure with a delay of the venous drainage. However, more cases are required to confirm the validity of this conclusion.
**Authors’ contributions**

Conception and design: Ahmed Sultan. Acquisition of data: Ahmed Sultan, Tamer Hassan, and Tamer Metwaly. Analysis and interpretation of data: Ahmed Sultan, Tamer Hassan, and Tamer Metwaly. Manuscript submission: Ahmed Sultan. Statistical analysis: Ahmed Sultan.

**Declaration of conflicting interests**

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**Ethical approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The research was accepted by the ethics committee of Faculty of Medicine Alexandria University Serial no. 03034516.

**Informed consent**

Informed consent was obtained from all individual participants included in the study.

**Availability of data and material (data transparency)**

Not applicable.

**Code availability (software application or custom code)**

Not applicable.

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