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Original Article

Long-Term Outcomes after Endovascular Obliteration of Pediatric Arteriovenous Malformation: A Multi-Center Analysis

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BACKGROUND: Although pediatric arteriovenous malformations (AVMs) are relatively rare, they carry a higher rate of rupture than in adults. Pediatric AVMs could also present with recurrent seizures or headaches. Endovascular embolization is usually achievable in pediatric AVMs with increasing complete obliteration rates, especially in cases with small AVMs. It also serves as adjuvant therapy with microsurgery or radiosurgery in larger AVMs. Long-term follow-up is required to confirm the efficiency of endovascular AVM obliteration, especially in young populations with the longest life expectancy.

OBJECTIVE: The aim of the study was to perform a multicenter analysis of embolized pediatric cerebral AVMs regarding the clinical and radiological outcomes with a long term follow up.

METHODS: A retrospective study of 57 pediatric patients diagnosed with cerebral AVMs and admitted to departments of neurosurgery at Alexandria, Sohag and Tanta University hospitals was conducted. All patients were subjected to clinical and radiological assessments. Endovascular embolization was done for all cases in one or two sessions. Complementary treatment included microsurgery and radiosurgery. Clinical and radiological follow-ups were done for all patients for at least one year. The outcome measures were angiographic disappearance of the AVM nidus and neurological improvement on clinical follow-up.

RESULTS: The study included 57 pediatric patients with age range between 4-18 years. Fifty-four patients (94.73%) presented with intracranial hemorrhage and 3 patients (5.26%) presented with seizures. All patients were treated with endovascular embolization as a primary modality of treatment. Total obliteration of the AVM was achieved in one session in 30 patients (52.63%) and in 2 sessions in 8 patients (14.03%). After endovascular embolization, 7 patients (12.28%) underwent microsurgical excision, and another 12 patients (21.05%) were referred to radiosurgery. All patients had no permanent morbidity or mortality related to the embolization technique. Five patients (8.77%) had transient neurological deficits. One patient had minimal subarachnoid hemorrhage (SAH) due to microwire perforation and another patient had temporary pulmonary edema due to the effect of dimethyl sulfoxide on lung; both patients improved with medical treatment. One patient had a retained tip of a microcatheter which was removed with surgery.

CONCLUSION: Endovascular embolization is a safe and effective technique as a single modality in the management of pediatric AVMs. It has extended the role of microsurgery and radiosurgery to treat previously non-curable high-grade lesions. Long-term follow-up over 3 years confirms stable occlusion. A longer follow-up is still needed due to the long life expectancy.

KEYWORDS: Endovascular embolization, Microsurgery, Onyx, Pediatric arteriovenous malformation, Radiosurgery.

INTRODUCTION

Arteriovenous malformations (AVMs) are infrequent vascular disorders, characterized by the presence of a nidus encompassing many irregular and tortuous blood vessel channels, connecting arteries (or arterioles) and veins (or venules) without an intervening capillary network. The most common complication of AVMs is hemorrhage, with a mortality rate reaching up to 15% and a morbidity rate of around 50%.[1] Most cerebral parenchymal AVMs are diagnosed between 20 and 40 years, and only around 20% of them are diagnosed before the age of 15 years.[2,3]

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However, a greater tendency to bleed is recognized for AVMs among young patients, with higher rates of major morbidity and mortality. In fact, pediatric AVMs represent the most common cause of spontaneous intracerebral hemorrhage (ICH) in children.[4,5] Pediatric AVMs may present with recurrent headaches and/or seizures.[6] Also, the nidus in pediatric AVM cases has been noted to have a higher occurrence of linear, vein-based malformations in contrast to the compact type in adults.[7]

The diagnosis of pediatric AVMs is dependent mainly on imaging studies, including computed tomography (CT) or CT angiography (CTA) and magnetic resonance imaging (MRI) or MR angiography (MRA). The CT/CTA evaluates the location and size of the hematoma while MRI/MRA is helpful in localization and therapy planning. However, conventional digital subtraction angiography (DSA) is still the gold standard technique for the diagnosis of AVMs and can help in the description of the AVM size, site, feeding arteries and draining veins, as well as the location of the nidus and any related vascular lesions.[8]

Endovascular embolization is achievable in pediatric AVMs with the potential of completely obliterating small AVMs or as a successful adjunctive treatment with microsurgery or radiosurgery in larger AVMs.[8,9] The value of endovascular embolization of AVMs gained popularity and higher success with time. Early studies demonstrated a cure rate from embolization of less than 20%, while other later studies showed that up to 94% success rate could be achieved with embolization alone.[10-12]

The current study aims to analyze the clinical and radiological outcomes and the long-term results of pediatric AVMs treated by embolization in a sample of Egyptian children.

PATIENTS AND METHODS

This retrospective study included 57 pediatric patients who were admitted to the departments of neurosurgery at Tanta, Sohag and Alexandria Universities between January 2010 and December 2018. All patients' parents were informed about the benefits and the risks of the intended procedure and an informed written consent was signed at least 24 hours before the operation. The study was conducted with the approval of the Research Ethics Committee, Faculty of Medicine, Sohag University on 08-09-2021. Institutional Review Board Number is (soh-med-21-09-50).

All patients were subjected to clinical and radiological assessments including MRI and CT/CTA as the primary modality of diagnosis. Endovascular embolization was done for all cases in one or more sessions. Complementary treatment included microsurgery which was performed based on the presence of large intracerebral hematoma, superficially located lesions, grades I and II AVMs, and patients' preference. Radiosurgery was planned in patients with deeply located lesions, grades III and IV AVMs, patients unfit for surgery, and according to patients' preferences. Clinical and radiological follow-ups were done for all patients for at least one year. Surgical management included evacuation of hematomas with mass effect and midline shift and insertion of ventriculo-subgleal shunts or sometimes ventriculoperitoneal shunts for patients with acute hydrocephalic changes.

All patients were treated with endovascular embolization as primary modality of treatment. Under general anesthesia, standard trans-femoral approaches were applied in all patients using 5 French and sometimes 6 French femoral sheaths. We have used 5 French in multipurpose diagnostic angiography for all patients. The DSA gives an accurate description of AVMs including size, location, feeding vessels, draining veins, location of the nidus and the presence of any associated vascular lesions. Replacement with 5 French and sometimes 6 French guiding catheters were done in all cases. Combination of different microcatheters and microwires were used according to diameter of feeders and target point of injection (single compartment nidus). Each compartment has only one draining vein, and this should be the target during injection.

Combinations of embolic materials were used including different liquid embolic agents. N-butyl cyanoacrylate (NBCA) or histoacryl (Trufill; Cordis, Miami Lakes, FL) is an adhesive glue that should be diluted in lipiodol contrast agent in different concentrations. Recently, Onyx (Medtronic; USA) is a non-adhesive premixed ethylene vinyl-alcohol copolymer dissolved in dimethyl-sulfoxide (DMSO) and suspended micronized tantalum powder. The non-adhesive liquid embolics give more time for injection, and better penetration of the nidus. Coils were used sometimes in cases with large fistula to occlude or dump high flow then they were followed by injection of liquid embolic. Recent microcatheters with detachable tip were used in combination with new liquid embolics to have more time and to avoid catheter sticking to the cast. Control DSA was performed at the end of the procedure, to evaluate the compartmental embolization and the future need for more sessions.

Immediate post embolization CT was needed after discharge from the angiography suite and another CT was performed at hospital discharge. Clinical and radiological evaluation by MRI/MRA was done at follow-up visits, depending on the primary result achieved. Patients who were scheduled for more sessions were planned to have them after 3-6 months. Patients planned for complementary microsurgery or radiosurgery were sent as soon as possible.

Statistical analysis was done using excel. Descriptive analyses were performed to characterize the distributions of variables. The analyses were conducted using frequencies for binary and categorical variables.

RESULTS

The mean age of our study population was 12±4.5 years (range: 4-18 years). The current study included 37 females (64.91%) and 20 males (35.09%). Fifty four patients (94.73%) presented with intracranial hemorrhage and 3 patients (5.26%) presented with seizures **(Table 1)**. All patients were treated with endovascular embolization as the primary modality of treatment. Total endovascular obliteration of the AVM nidus was achieved in 38 patients (66.67%). Total obliteration of the AVM was achieved in one session in 30 patients (52.63%) and in 2 sessions in 8 patients (14.03%). Nineteen patients (33.3%) had residual after endovascular embolization. Seven patients (12.28%) had complementary microsurgery; these included 3 patients with Spetzler-Martin grade 2, 2 patients with grade 3, 1 patient with grade 4 and 1 patient with grade 5. Twelve patients (21.05%) had complementary radiosurgery; these included 3 patients with Spetzler-Martin grade 2, 8 patients with grade 3 and

1 patient with grade 4.

All patients had no permanent morbidity or mortality related to the embolization technique. Complications occurred in 8 patients (14.03%); 5 patients (8.77%) had transient neurological deficits that improved spontaneously, one patient (1.75%) had minimal SAH due to microwire perforation, another patient (1.75%) had temporary pulmonary edema due to the effect of DMSO on lung, both patients improved with medical treatment, and the last patient (1.75%) had a retained tip of microcatheter which was removed with surgery **(Table 2).**

The mean follow-up period was 3.5 years (1-6 years). All patients treated with endovascular embolization came for a regular clinical and radiological follow-up with MRI/MRA at 3 months, 6 months, then annually. Three patients had additional diagnostic angiography during the period of follow-up. None of our patients showed any residual or recurrence during the follow-up period **(Fig. 1-4)**. The 3 patients who presented with seizures had controlled seizures after intervention. One patient stopped his antiepileptic drugs after 6 months, and the other 2 patients required continuation of their antiepileptic medications

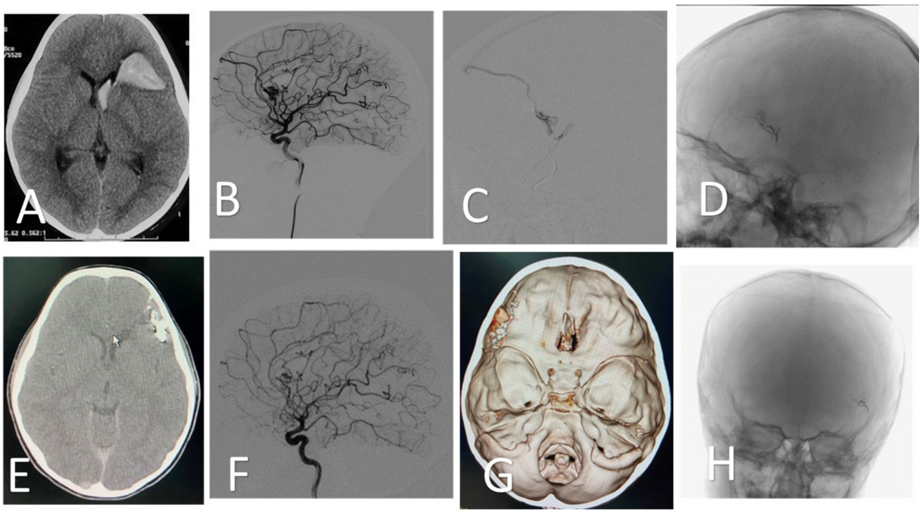

Fig 1: Male child, 8 years old, presented with left frontal ICH with intraventricular extension. CTA shows small frontal AVM. Endovascular embolization performed in one session with total obliteration of AVM. (A) CT brain at onset shows ICH with intraventricular hemorrhage (B) Pre-embolization lateral left carotid angiogram shows the feeding artery (anterior cerebral artery), nidus and draining vein (C) Super-selective catheterization of the feeding artery (D) Onyx cast in the 1st view takes same configuration of the nidus (E) Onyx cast in post-embolization CT with complete resolution of the hematoma (F) Post-embolization lateral left carotid angiogram shows total obliteration of AVM (G) Onyx cast in post-embolization 3 dimensions bone window CT (H) Onyx cast in X-ray anteroposterior view.

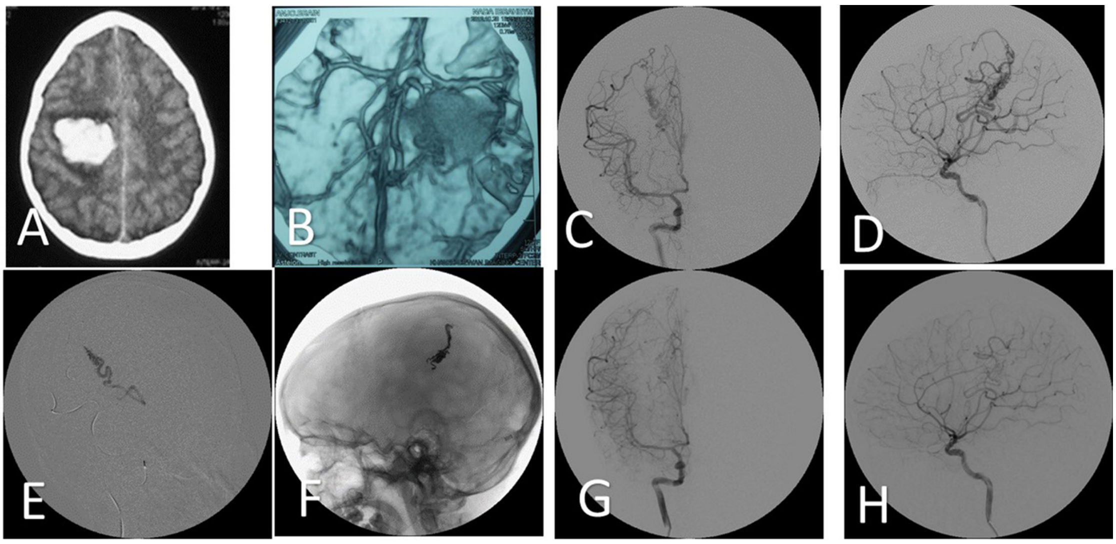

Fig 2: Female child, 10 years old, presented with right fronto-parietal ICH with intraventricular extension. CTA shows small Rolandic AVM. Endovascular embolization performed in one session with total obliteration of AVM. (A) Axial CT brain shows ICH (B) CTA shows small AVM and ICH (C&D) Right internal carotid artery angiogram shows AVM with feeders from Rolandic and medial lenticulostriate arteries (deep part) (E) Super selective catheterization of Rolandic artery shows nidus of AVM (F) Fluoroscopic image anteroposterior view shows Onyx cast strictly intranidal (G&H) Right internal carotid artery angiogram shows obliteration of AVM with penetration of embolic material to deeper part and foot of the vein.

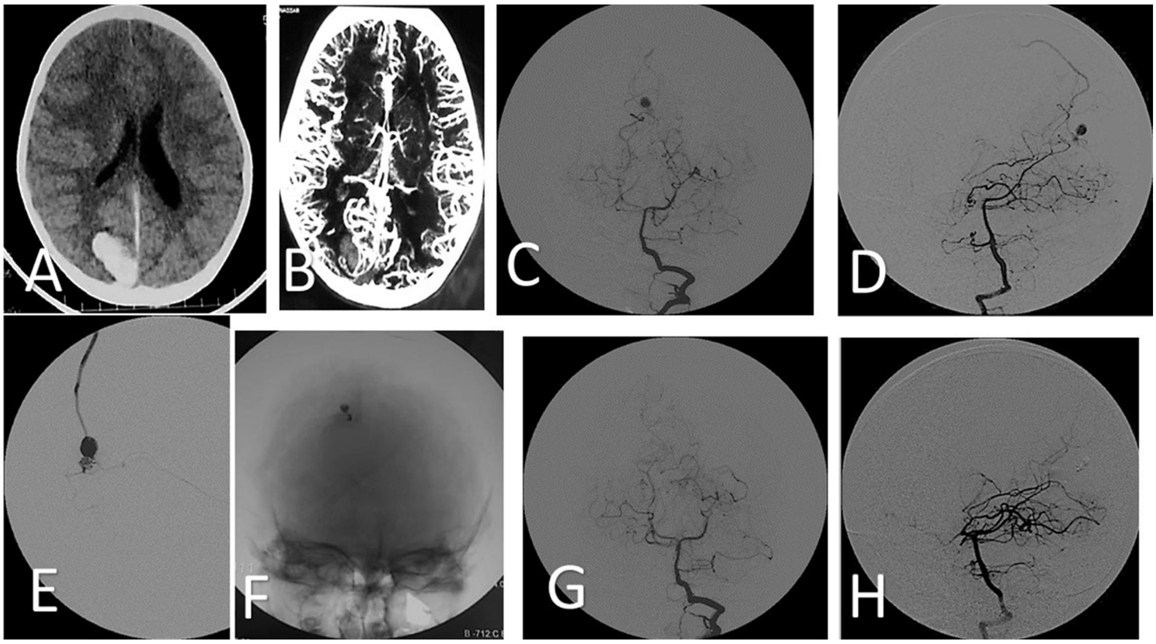

Fig 3: Female child, 7 years old, presented with right occipital ICH. CTA shows small occipital AVM with nidal aneurysm. Endovascular embolization performed in one session with total obliteration of AVM & nidal aneurysm. (A) Axial CT brain shows ICH (B) CTA shows right occipital small AVM and ICH (C&D) Left vertebral angiogram shows small occipital AVM & nidal aneurysm (E) Super selective catheterization of the feeding artery (F) Fluoroscopic image shows glue cast in nidus and aneurysm (G&H) Control left vertebral angiogram shows total obliteration of both AVM and nidal aneurysm.

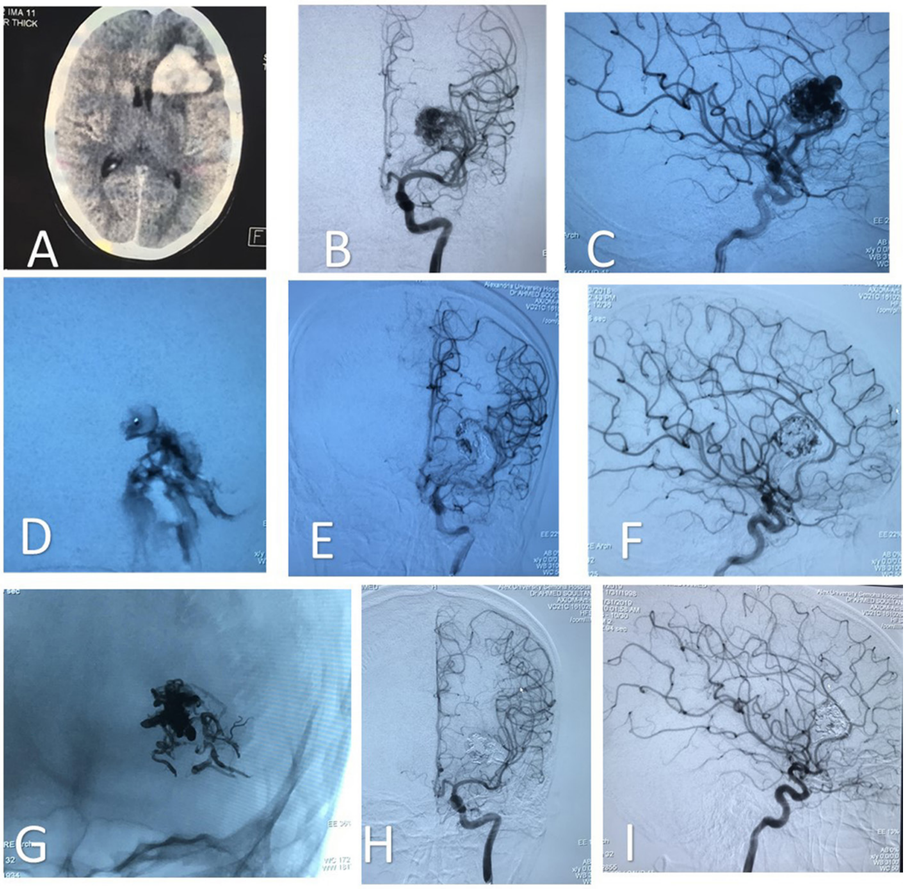

Fig 4: Female child, 17 years old, presented with left frontal ICH. CTA and MRI showed left frontal AVM. Endovascular embolization performed in one session with near total obliteration of AVM. (A) Axial CT brain shows ICH (B&C) Left internal carotid artery angiogram shows the AVM with nidal aneurysm supplied by middle cerebral artery branches (D) Super selective angiogram with contrast leak (E&F) Control left internal carotid artery angiogram shows near total obliteration of both AVM and nidal aneurysm (G) Plain X-ray showing the Onyx cast (H&I) Follow up angiogram of the left internal carotid artery showing complete disappearance of the AVM after 12 months.

Table 1: Demographics and presentation of the study group

		No (%)
Gender	Female	37 (64.91%)
	Male	20 (35.09%)
Presenting finding	Isolated ICH	32 (56.14%)
	ICH with intraventricular extension	6 (10.52%)
	ICH with subarachnoid smearing	5 (8.77%)
	Isolated intraventricular hemorrhage	11 (19.29%)
	Fits	3 (5.26%)
Location	Frontal	13 (22.80%)
	Parietal	16 (28.07%)
	Occipital	12 (21.05%)
	Temporal	5 (8.77%)
	Posterior fossa	4 (7.01%)
	Intraventricular	3 (5.26%)
	Thalamic	2 (3.50%)
	Callosal	2 (3.50%)

ICH: intracerebral hemorrhage.

Table 2: Outcome and complications of the study group

		No (%)
Outcome	Total obliteration of AVMs in one session	30 (52.63%)
	Total obliteration of AVMs in 2 sessions	8 (14.03%)
	Microsurgery	7 (12.28%)
	Radiosurgery	12 (21.05%)
Complications	Transient hemiparesis	5 (8.77%)
	Hemorrhage	1 (1.75%)
	Temporary pulmonary edema	1 (1.75%)
	Retained microcatheter	1 (1.75%)

AVM: arteriovenous malformation.

DISCUSSION

Cerebral AVMs are uncommon lesions with an overall prevalence of less than 1%. Prevalence in pediatric patients is even less, ranging from 0.01 to 0.03%. Hemorrhage is the most frequent clinical manifestation of cerebral AVMs and occurs in nearly 75% of the patients. However, children have a specific high risk for hemorrhagic events as compared to adults, with up to 85% of children presenting with an episode of intracranial bleeding. The angioarchitecture of cerebral pediatric AVMs have some differences from the adult ones. These differences include preponderance of venous anomalies, large pial fistulas and brain immaturity. Cerebral AVMs have more concerns in children due to longer life expectancy and the higher annual incidence of hemorrhage in children than in adults. In addition, the preponderance of large parenchymal bleeding is common in those young populations.[2,13-15]

Children are not young adults, and the management protocols of the adult populations may not be suitable for them. However, these approaches may be applied with suitable modifications. The treatment of pediatric AVMs has 4 lines of treatment as the adult ones. These include conservative, endovascular, microsurgical and stereotactic radiosurgical modalities. No randomly controlled trials were done to optimize treatment options and make a guideline. The rarity of these lesions made these trials impossible. The consensus on the best treatment is never available, being debatable and challenging. Even the ARUBA (A Randomized trial of Unruptured Brain Arteriovenous malformations) trial carries great controversy and its recommendations on non-ruptured brain AVMs are not followed by most centers. The young population has a long-life expectancy which necessitates solid decision-making in the case of brain AVMs that carries a non-negligible risk of rupture at any point of their lives.[1-5,13]

Our study included 57 pediatric cases, most of them with hemorrhagic AVMs, and it aimed to analyze the pattern and outcome of these cases in pediatric Egyptian population. The mean age of our study population was 12±4.5 years. Our cases were somewhat older than those studied by Blauwblomme et al. where the mean age of their cases was around 10 years (116 months),[16] and LoPresti et al. where the mean age was around 9.8 years.[17] Cases of Mendes et al. and Park et al. were older than ours, with a mean age of 13-13.5 years.[18,19] There was slight female preponderance (64.91%) among the current study cases. This was similar to the study of Mendes et al. who reported slight female preponderance among their cases.[18] On the other hand, the study of Blauwblomme et al. showed slight male preponderance (58.5%),[16] and the studies of Di Rocco et al. and Park et al. showed similar male preponderance.[2,19]

At time of admission, fifty four (94.73%) patients presented with intracranial hemorrhage and only 3 (5.26%) presented with seizures. In the study of Park et al. most of the cases (53/68) presented with hemorrhage, while only 9 cases presented with seizures and 6 cases presented with headaches.[19] Locations of the AVMs in our series were frontal in 13 patients (22.80%), parietal in 16 patients (28.07%), occipital in 12 patients (21.05%), temporal in 5 patients (8.77%) and posterior fossa in 4 (7.01%) patients. The frontal predominance was found in the study of LoPresti et al. where they stated frontal involvement in 40% of the cases, followed by parietal (26%), and temporal (24%) lobes.[17] The study of Mendes et al. showed somewhat different distribution, where 2 out of their 7 cases had either frontal, temporal or corpus callosum location and the seventh case had parietal hemorrhage.[18] Di Rocco et al. stated that temporal location was the most common one among their cases, followed by parietal, frontal, cerebellar and finally brainstem.[2]

All patients in the current study were treated with endovascular embolization as the primary modality of treatment. Around 67% of the cases had total obliteration of the AVMs in 1 or 2 sessions, while 33% needed either microsurgery or radiosurgery. This was totally different from the study by Di Rocco et al. where surgery (with or without radiosurgery) was done in around 90% of the cases either alone or combined with endovascular embolization.[2] At the beginning of AVM treatment, microsurgery was the main line with considerable mortality and morbidity especially in high grade lesions. Radiosurgery was indicated in small deep-seated lesions. The great progress in endovascular materials, development of flow directed microcatheters, efficient microwires and liquid embolics led to maximization of the role of embolization. Recent studies have reported that standalone endovascular embolization was associated with complete cure in more than 50% of cases, while old ones reported only 5-20% cure with embolization.[20-22] This was mostly due to embolization being used previously as an adjuvant treatment and not for curable aims. Also, initial embolic agents like polyvinyl alcohol particles and old microcatheters were not helpful to fill the AVM nidus in a safe and a permanent way, thus recanalization was very high. Recent liquid embolic agents like NBCA and Onyx are permanent agents without any recanalization in the obliterated compartment of the AVM nidus. In our study complete angiographic obliteration with endovascular embolization reached 67%. As adjuvant treatment, embolization greatly facilitated microsurgery and extended the role of radiosurgery to larger lesions. The blood loss during microsurgery was decreased by obliterating the arterial feeders, especially deep ones. Microsurgery of AVMs became as easy as tumor surgery after embolization.[3,4,6]

Embolization-related complications occurred in 8 patients; 5 patients had transient neurological deficits, and 3 patients had other controllable complications; one patient had temporary pulmonary edema, one patient had minimal SAH, and the last patient had a retained tip of microcatheter. There were no permanent deficits or deaths. In the study of Park et al., complications occurred in 6 out of 68 cases including adverse radiation effects in 3 patients, hydrocephalus in 2 patients, and hemorrhage in one patient.[19] The study of LoPresti et al. showed that the main complications of non-surgically treated cases included rupture in 6 patients, hydrocephalus in 6 patients and neurological deficit in 3 patients out of the total of 35 cases.[17] Embolization-related complications were usually transient and very low. They were reported in a comparable percent to those occurring after microsurgery or radiosurgery.

The mean follow-up period in the current study was 3.5 years with the follow-up period reaching up to 6 years. None of our patients showed residual or recurrence during the follow-up period. Similarly, the study of Mendes et al. showed a 100% success with no recurrence during the follow-up period.[18] In the study by Blauwblomme et al., 8 patients (7.5%) out of their 106 cases experienced recurrence of bleeding during the follow-up period.[16] Obliterating or vanishing of the AVM nidus is the main aim of any modality. Also, long-term follow-up is necessary to validate the treatment option especially in those young patients with long-life expectancy. Previous reports showed follow-up reaching about 11 years after embolization.[20,21]

A single modality treatment is never enough for all AVMs treatment; each modality has its own success and failures. Grades I and II AVMs carry the best opportunity for cure even with a single modality. Grades III, IV and V are not amenable to a single modality. Endovascular embolization plays an important role as an adjuvant treatment to both surgery and radiosurgery. It increases the rate of cure in combination with other modalities. Complete nidal exclusion is the best protector against the lethal and morbid effect of AVMs in those young patients with long-life expectancy. However, there is rare incidence of recurrence reported even after complete excisions or eradication of cerebral AVMs with negative DSA. The recurrence may be due to occult lesions, angiogenesis, hidden compartments, and the dynamic nature of the AVM.[23,24] Long-term follow up for years is warranted to detect any recurrence.

CONCLUSION

Endovascular embolization is a safe and effective technique as a single modality in management of pediatric AVMs. It has extended the role of microsurgery and radiosurgery to treat previously non curable high-grade lesions. Long-term follow-up over 3 years confirms stable occlusion. A longer follow up is still needed due to long life expectancy.

List of abbreviations

ARUBA: A Randomized trial of Unruptured Brain Arteriovenous malformations.
AVM: Arteriovenous malformation.
CT: Computed tomography.
CTA: Computed tomography angiography.
DSA: Digital subtraction angiography.
ICH: Intracerebral hemorrhage.
MRA: Magnetic resonance angiography.
MRI: Magnetic resonance imaging.
NBCA: N-butyl cyanoacrylate.
PVA: Poly vinyl alcohol.
SAH: Subarachnoid hemorrhage.

Disclosure

The authors report no conflict of interest in the materials or methods used in this study or the findings specified in this paper.

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