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Research article

Safety and outcome of combined endovascular and surgical management of low grade cerebral arteriovenous malformations in children compared to surgery alone☆

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ABSTRACT

Purpose: To evaluate the outcomes of combined preoperative embolization and microsurgical resection in comparison with microsurgical resection alone as the current standard of care for low-grade cerebral arteriovenous malformations (AVM) in the pediatric population.

Materials & methods: We performed a single-center retrospective study of pediatric patients presenting with Spetzler-Martin (SM) grade I and II cerebral AVMs at a high-volume tertiary pediatric hospital between January 2005 and September 2016. Low grade AVM patients were divided into two groups: pre-operative embolization with subsequent microsurgical resection or microsurgical resection alone. Patient demographics, clinical and imaging presentations, AVM morphological characteristics, post-operative complications, and mid to long-term clinical outcomes were studied. Post-embolization and post-surgical outcomes were assessed prior to and after treatment, at 3 months and at final follow-up using the modified Rankin Scale (mRS) to compare both final independent (mRS 0–2) and favorable (no change or improved mRS) clinical outcomes for comparison between study groups. Statistical associations of patient demographics, AVM characteristics/SM grading, and treatment modality group with post-operative complications were performed using univariate logistic regression analysis.

Results: Thirty-four patients with low grade cerebral AVMs met the study inclusion criteria (mean age 10.6 ± 3.4 years; range 3–16 years, 22M:12 F). Twenty patients (59%) presented with ruptured AVMs. Twenty-five patients (73.5%) underwent combined treatment with embolization and microsurgical resection, while 9/34 (26.5%) underwent microsurgical resection alone. A total of 35 embolization procedures performed in 25 patients (Mode, 1; Range, 1–7) were associated with two minor post-embolization and 7 subsequent post-surgical (28%) complications, resulting in clinical deterioration in a single patient. Microsurgical resection alone was associated with 3 post-surgical complications (33%), resulting in permanent neurological disability in a single patient. There was no significance association of post-operative complications with either treatment modality group, combined treatment versus surgical resection alone [OR:1.13; 95% CI:0.23–5.62; p-value 0.88]. SM Grade II and eloquent locations were found to be significantly associated with post-surgical complications of low grade pediatric cerebral AVMs [OR 13.2 and OR 8 respectively, p-value 0.004 and 0.005). On mean follow-up time of 35.7 months, final clinical outcome was favorable in the majority of both treatment arms with no dependent (mRS > 2) patients in the combined endovascular and surgical cohort. Two patients in the surgical cohort failed to achieve independent functional status, primarily due to a pre-operative morbid status (p-value 0.015). However, there was no significant difference in favorable outcomes between the treatment groups [p-value 0.14].

Conclusion: Our study suggests equivalent safety and favorable clinical outcomes related to combined endovascular embolization and microsurgical resection of low grade pediatric cerebral AVMs in comparison to

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microsurgical resection alone. On long term clinical follow-up, the vast majority of patients achieved an independent and favorable functional status irrespective of pre-operative embolization.

1. Introduction

Cerebral arteriovenous malformations (AVMs) are a complex network of direct arteriovenous shunts with an absence of the normal intervening capillary bed. The etiology and natural history of AVMs are still not clearly understood. Cerebral AVMs are persumed to be congenital lesions which occur during embryonic development [1,2], although multiple cases of de novo pial AVMs have been reported [3]. AVMs usually present in the second to fourth decade of life, with a mean age at presentation of 34 years. Intracranial hemorrhage is the most common overall presentation, occurring in approximately 52% of all cases [4], compared to an incidence of 69% in children as estimated by a recent multicenter pediatric cohort [5]. Low grade AVMs (SM Grade I and II) accounted for approximately 37% of the ruptured AVMs in the pediatric multicenter study.

AVMs are considered the primary etiology of hemorrhagic stroke in children [6], with a reported annual hemorrhage risk of 6.3% and re-hemorrhage risk of 14.8% [5], which is significantly higher than the overall annual hemorrhage and re-hemorrhage risk in adults of 3% and 4.5% respectively [4]. Additionally, increased neuroplasticity in children may reduce the morbidity of interventional, endovascular and surgical, procedures [7]. Along with an inherent long life expectancy, there may be stronger indications to intervene in the pediatric population even in unruptured AVMs.

With rapid technological advancements in endovascular techniques, embolization is now recognized as one of several treatment modalities that alone or in combination with other treatments, can significantly improve the outcome of cerebral AVM interventions [8,9]. However, the role of embolization in the management of Spetzler Martin (SM) Grade I and II AVMs is considered debatable or unnecessary in the neurovascular surgery literature, given the relatively low morbidity and mortality of microsurgical resection alone.

In pediatric tertiary institutions, patients are often treated by highly skilled pediatric neurosurgeons, rather than dedicated neurovascular surgeons as in adults. At our institution, the preference of our neurosurgeons has been for pre-operative embolization prior to microsurgical resection. In this study, we reviewed and analyzed our treatment of low SM Grade I and II AVMs, with an emphasis on immediate post-operative complications and final clinical outcomes related to microsurgical resection alone versus combined multimodal treatment with pre-operative embolization and microsurgical resection. Furthermore, we present our case series and results in the context of reviewing the previously published literature.

2. Methods

Institutional review board approval was obtained for a retrospective study of pediatric patients who presented to our institution between January 2005 and September 2016 with SM grade I and II pial cerebral and cerebellar AVMs. Patients with vein of Galen malformation, dural/pial arteriovenous fistulas (AVF), extracranial scalp or head/neck AVMs were excluded from this study. A total of 41 patients were initially identified, but 34 patients met the interventional inclusion criteria of embolization and/or microsurgical resection after excluding 2 patients treated with stereotactic radiosurgery, 2 patients that underwent microsurgical resection at an outside institution, 1 patient who was cured after embolization alone, and 2 patients lost to follow-up.

Inpatient/outpatient and physical therapy medical records, diagnostic and follow-up imaging were reviewed for patient demographics, clinical and imaging presentations, AVM morphological characteristics, post-embolization/post-operative complications, and mid to long term clinical outcomes. Conventional Digital Subtraction Angiography (DSA) was available in all 34 patients to confirm the diagnosis and angioarchitecture of AVMs for SM grading, retrospectively by an experienced interventional neuroradiologist. The level of disability pre-operatively, post-operatively, on 3 month and final clinical follow-ups were assessed using the modified Rankin Scale (mRS) [7]. Immediate worsening of a pre-existing/presenting neurological deficits or pre-operative (baseline) mRS was considered a major post-embolization or post-operative complication. The final clinical outcome was considered dependent (disabling neurological deficit) if the final mRS Score was > 2 and unfavorable if there was any increase in the baseline mRS.

2.1. Statistical analysis

Treatment results, in terms of post-embolization/post-operative complications and final clinical outcomes, were compared between the two treatment groups: combined embolization-surgery versus surgery alone. The association of treatment modality with both the final absolute level of disability as well as favorable clinical outcomes (improved or static mRS score) were analyzed using Chi-square test. To control the effect potential confounding factors, ruptured versus non-ruptured and poor versus good preoperative/baseline mRS scores stratified analyses were calculated. Univariate logistic regression analyses were used to describe the effect of sex, presentation (ruptured vs. non-ruptured), pre-operative neurological status, SM grade, nidus size, presence of deep venous drainage, eloquent location, and treatment modality on the rate of post-operative complications. STATA 12.1 was used to run the calculations.

3. Results

3.1. Patient demographics/presentations and AVM characteristics

This study included a total of 34 patients with a mean age 10.6 ± 3.4 years (range 3–16 years). The male to female ratio was 1.8:1 (Table 1). Twenty patients (59%) presented with ruptured AVMs. Of the ruptured AVMs, 15 patients presented with headache (75%), 1 patient presented with seizure (5%), 2 with focal neurological deficits (10%), and 5 with decreased level of consciousness (25%). Of the unruptured AVMs 4 presented with headache (29%), 2 with seizure (14%), 1 with decreased mental status (7%), and 6 were discovered incidentally (43%). The most common presenting symptom was headache in 19 patients (56%) and of these 15 were secondary to an intracranial hemorrhage. Clinical presentations of all patients are shown in Appendix A.

Of the 34 patients, seven patients (21%) had poor neurological function status (mRS > 2) pre-operatively. Thirteen AVMs were characterized angiographically as SM grade I (38%) and 21 were SM grade II (62%): 27 with a small < 3 cm nidus (79%); 4 with deep venous drainage (12%); 12 in eloquent locations (35%); and only 2 lesions were infratentorial (6%).

3.2. Treatment modalities

A majority of patients 25/34 (73.5%) underwent combined treatment with pre-operative embolization and microsurgical resection, while 9/34 (26.5%) underwent microsurgical resection alone. Patients presenting with AVM rupture/intracranial hemorrhage comprised 8/9 patients (89%) who underwent microsurgical resection alone and 12/

Table 1
Demographics, Clinical, and Morphological characteristics.

Mean age at presentation (Range)	10.6 ± 3.4 (3–16)
Sex M/F	22/12
Mode No. of Embo procedures (range)	1 (1–7)
Hemorrhagic Presentation	20 (59%)
Treatment	
Combined Treatment (Pre-operative Embo + Surgical	25 (73.5%)
Resection)	9 (26.5%)
Surgical Resection	
Symptoms at Presentation:	
Incidental	6
Headache [without hemorrhage]	19 [4]
Seizure [without hemorrhage]	4 [2]
Focal Neurological Deficits	2
Deterioration of LOC	6
Change Mental Status	1
Spetzler Martin Score:	
Grade I	13 (38%)
Grade II	21 (62%)
Nidus	
Site	32
Supratentorial	
Infratentorial	2
Size	27 (79%)
< 3 cm	
3–6 cm	7 (21%)
Pre-operative mRS	
0–2	27 (79%)
> 2	7 (21%)
Deep Venous Drainage	4 (12%)
Eloquent area	12 (35%)

25 patients (48%) who underwent combined treatment. Out of 20 patients who presented with intracranial hemorrhage, 9 patients (45%) required surgical decompression prior to definitive AVM treatment and of these only 1/9 patients underwent surgical decompression and AVM resection in the same operation (11%) and 4/9 patients underwent microsurgical resection alone without embolization (44%). A total of 35 embolization procedures were performed in 25 patients, with a mode of 1 embolization procedure per patient. Ethylene vinyl alcohol (Onyx, Medtronic) was utilized in all embolization procedures except one and N-butyl cyanoacrylate (TRUFILL n-BCA, Cordis Neurovascular) was employed in 2 procedures.

3.3. Treatment complications and clinical outcomes

Two embolization related complications (transient vessel perforation in patient 8 and groin hematoma in patient 16; Appendix A) were encountered (2/25, 8% of patients or 2/35, 5.7% of procedures), with no neurological sequelae in both patients. None of the patients had an increase in their baseline mRS following embolization procedure. Furthermore, 10/34 (30%) patients suffered neurological complications after AVM resection. In the combined embolization-microsurgical resection cohort, 7 post-surgical neurological deficits/seizures (7/25, 28%) occurred; one resulting in clinical deterioration from mRS 0 to 1 (patient 16) on final clinical follow-up. In the microsurgical resection alone cohort, three neurological complications were observed (3/9, 33%); one of them resulting in permanent neurological disability (patient 21).

Despite mean follow up time of 35.7 months (Range 3–97 months), nearly all 33/34 patients (97%) reached their final mRS score within 3 months of surgical AVM resection. On final clinical follow-up, all 25/25 patients in the combined treatment cohort versus 7/9 patients in the surgery alone cohort demonstrated an independent functional outcome (mRS 0–2) [p-value 0.015], but this was not significant when accounting for the higher baseline pre-operative mRS in the surgery alone cohort. There was deterioration in mRS score of 1 patient in the combined treatment group, though the patient remained functionally independent (mRS 1), as well as mRS deterioration of 1 patient in the surgery alone group (unfavorable outcomes). Hence, there was no significant difference in the overall favorable outcomes between the two treatment groups (no change or improved mRS score) [p-value 0.14] (Table 2). There was no significant difference in final independent or favorable outcomes when accounting for patients presenting with ruptured versus non-ruptured AVMs [p-values 0.81/0.49] (Table 3), or with poor versus. good preoperative/baseline mRS scores [p-value 0.53/0.36] (Table 4) between the treatment groups.

3.4. Associations of patient demographics/AVM characteristics and treatment modality with complications

It was possible to perform univariate analysis using simple logistic regression (Cut-off, p-value < 0.25) on all AVM parameters, except nidus site (supratentorial vs. infratentorial) as shown in Table 5. This analysis showed no significant association of the modality of treatment of low grade AVMs with complications, either combined embolization and microsurgical resection [OR:1.13; 95% CI:0.23–5.62; p-value 0.88. SM grade II and eloquent AVM location were associated with significantly higher risk of post-surgical treatment complications; (OR 13.2, p-value 0.004) and (OR 8, p-value 0.005) respectively. The patient's level of disability (mRS score) prior to the initiation of either treatment modality did not affect complication rates (p-value 0.64)

4. Discussion

Intracranial hemorrhage is the most common presentation for pediatric AVMs. Our single-center retrospective study showed 59% of pediatric low grade cerebral AVMs presenting with an intracranial hemorrhage, which is similar to the reported literature ranging from 57%–86.1% across multiple studies [10–15]. However, we had an insufficient number of infratentorial low grade AVMs in our study population, which may be attributed to tertiary center referral bias. Prior literature indicated that infratentorial AVMs are independently associated with hemorrhagic presentation and worse clinical outcomes [16,17], and these patients may not have been transferred to our institution.

The annual hemorrhagic risk from pediatric unruptured AVMs is estimated at 6.3%, significantly higher than in adults (2–4%) [[18]]. The longer life expectancy of children further increases their risk of AVM rupture and intracranial hemorrhage according to the formula: $Risk\ of\ hemorrhage = 1 - (risk\ of\ no\ hemorrhage)^{expected\ years\ of\ remaining\ life}$ [19] Ma et al in their retrospective study reported that 49% of children with AVM rupture presented with severe disability (mRS > 3) and/or required emergency hematoma evacuation [20]; compared to 60% in our study of low grade AVMs. The higher annual risk of AVM rupture with associated increased complications and morbidity as well as the significant cumulative lifetime risk in children demonstrates the value of AVM obliteration in this population. Previous studies have demonstrated favorable clinical outcomes after pediatric AVM treatment

Table 2
Neurological Outcomes.

Measure and Results	Patients of Embolization + Surgery group	Patients of Surgery alone group	Total no. of patients
Final mRS			
Good*	25	7	32
Poor	0	2	2
Change (mRSΔ)			
Improved or unchanged[i]	24	8	32
Deterioration	1	1	2

* p-value: 0.015.
[i] p-value:0.14.

Table 3
Neurological Outcome in patients with pre-op mRS > 2.

Measure and Results	Patients of Embolization + Surgery group	Patients of Surgery alone group	Total no. of patients
Final mRS			
Good*	2	3	5
Poor	1	1	2
Change (mRSΔ)			
Improved or unchanged[i]	2	4	6
Deterioration	0	1	1

* p-value: 0.81.
[i] p-value:0.49.

Table 4
Neurological Outcome in patients with Ruptured AVMs.

Measure and Results	Patients of Embolization + Surgery group	Patients of Surgery alone group	Total no. of patients
Final mRS			
Good*	12	7	19
Poor	0	1	1
Change (mRSΔ)			
Improved or unchanged[i]	11	8	19
Deterioration	1	0	1

* p-value: 0.53.
[i] p-value:0.36.

Table 5
Univariate logistic regression showing the association of demographics, AVM characteristics, treatment modality with complications.

Characteristic	Frequency	OR (95% CI)	p-value
Age	34 (mean 10.6 Y)	0.82 (0.65–1.03)	0.07
Female (vs. male Gender)	12 (35%)	1.53 (0.36–6.57)	0.56
Combined Treatment modality (Embolization + Surgery) (vs. microsurgical resection alone)	25 (73.5%)	1.13 (0.23–5.62)	0.88
Spetzler Martin Grade II (vs. Grade I)	21 (62%)	13.2(1.44–120.62)	0.004
Deep venous drainage (any)	4 (12%)	0.58 (0.05–6.23)	0.64
Nidus Size 3-6 cm	7 (21%)	0.47 (0.07–2.82)	*0.41*
Ruptured Presentation	20 (59%)	0.57 (0.14–2.38)	0.44
Eloquent location	12 (35%)	8 (1.8–45)	0.005
Poor mRS score at presentation(> 2)	7(21%)	1.50 (0.27–8.19)	0.64

relative to adults [21,22], which may be attributed to greater neuroplasticity in children [21].

Although the ARUBA trial suggested the superiority of conservative management particularly in unruptured AVMs, this trial excluded pediatric AVMs and was not limited to low SM grade lesions, typically associated with lower surgical morbidity. A recent cohort study by Wong et al. [23] evaluating microsurgical resection in 155 ARUBA-eligible patients and another systematic review by Potts et al. [24] studying the microsurgical resection of low grade unruptured AVMs (with or without pre-operative embolization) identified excellent functional outcomes after intervention challenging the results of the ARUBA trial.

Endovascular embolization has been recognized as an established adjunctive treatment for the pre-operative devascularization of AVMs. It has been shown to be safe and effective in facilitating total surgical resection, reducing the risk of intra-operative bleeding, and potentially decreasing the risk of AVM recurrence [8,9,25]. The cure rate for pediatric brain AVMs after endovascular embolization alone varies from 4%–21.2%, with permanent clinical deficits ranging between 0%–2% [10,12,25–27]. In our study, the cure rate following embolization was 4% (1/26 patients), who was accordingly excluded from this study, and the post-embolization complication rate was 5.7% (2/35 procedures) to 8% (2/25 patients); none associated with permanent clinical or neurological sequelae. However, Castro-Afonso et al in their study with the intention to cure pediatric brain AVMs through embolization [9] reported a complete AVM occlusion in 21/23 patients(91.3%) and complication rate of 13%; none resulting in permanent morbidity or mortality. Recent advances in endovascular embolization techniques, particularly with the introduction of new liquid embolic agents (ethylene vinyl alcohol, Onyx, Medtronic), detachable tip microcatheters, dual lumen balloon microcatheters, transvenous embolization [28], and improved angiographic quality with low radiation dose have enabled safer and more effective AVM embolization with low complication rates.

Microsurgical resection remains the standard of care for the definitive management of low grade AVMs. The results of our study show no significant difference in complication rates or favorable clinical outcomes between the study groups. In fact, there was one disabling neurological complication (mRS > 2) after microsurgical resection alone, while no disabling neurological complications resulted from combined embolization and microsurgical resection. All patients in the combined treatment group had good functional outcomes (mRS ≤ 2) on final follow up, while 2 patients had poor functional outcomes (mRS ≥ 3) in the surgical only group, primarily related to pre-operative morbid status, one of whom had long-term poor baseline mRS score due to previous brain surgery. It is interesting to note that 70% of the neurological complications in this series occurred in patients who harbored AVMs in eloquent regions of the brain, consistent with previous studies demonstrating it to be an independent predictive factor for neurosurgical complications [29]. The current literature lacks studies comparing the outcomes of different modalities in the treatment of pediatric low grade cerebral AVMs. The reported complication rates after microsurgical resection alone in this population vary between 0%–25% [11,30–32], but there have been no reports addressing complications with combined management [11,31,32]. Our current study noted a nearly 28% combined embolization and microsurgical resection neurological complication rate versus 33% with microsurgical resection alone, albeit only 2/34 (5.9%) patients (1 from each group) suffered permanent neurological deterioration (unfavorable clinical outcome). Since there was no statistical difference in complication rates or favorable clinical outcomes between treatment groups or associations of either treatment modality with complications on logistic regression analysis, our data suggests the relative safety of adjunctive embolization in the management of pediatric low grade AVMs.

Four patients in this series presented with seizures (12%), two of which were associated with intracranial hemorrhage. The AVM nidus location in all patients presenting with seizures was in the frontal-temporal lobe distribution. All four patients were seizure-free during the follow up period (modified Engel Class 1), only two requiring anti-epileptics. In our study, 32 patients (94%) had a modified Engel class 1 outcome with only 1 post-operative seizure in a single patient, and two patients had a modified Engel class 2 outcome (6%). Our post-operative seizure outcomes are consistent with a large series by Englot et al. [33] and a recent pediatric series by Xiangke Ma et al [34] who reported post-surgical class 1 outcome of 96% and 91% versus the overall pre-operative seizure rates of 30% and 31.8%, respectively. However, the seizure rate that is attributed to low grade AVMs in both studies were 13.4% and 14% respectively, consistent with our findings and an indication that low grade AVMs are less likely to present with seizure.

Recurrence rates after complete surgical obliteration of brain AVMs in children varies in literature 0.6%- 15.9% [12,14,15,35–38], but with a predilection in pediatric patients [39] confirming that AVMs are not static lesions [40]. In a retrospective cohort study by Lang et al. [37], they reported no significant association between SM grade, nidus size,

or pre-operative embolization with the risk of recurrence in pediatric AVMs. A recent systematic review of 1052 articles by Jimenez et al. [41] revealed a significant greater risk of recurrent AVM rupture in pediatric patients without adequate follow-up, indicating the need for long-term post-operative imaging evaluations. In our series, we noted only 1 recurrent SM grade 1 AVM that was detected on follow-up imaging at 1 year after presumed complete AVM obliteration confirmed by DSA (case 11, Appendix A). Since inadequate or absence of clinical and imaging follow-up can increase the risk of recurrent AVMs related complications, we recommend immediate diagnostic cerebral angiography (DSA) following microsurgical resection to exclude a residual lesion, then imaging follow-up at 1 year, 3 years, 5 years and every 5 years until the age of 18. Similarly, Morgenstern et al. [39] proposed early imaging after AVM resections in pediatric patients with an intraoperative or early post-operative angiogram, followed by a DSA at 1 year, 3 years, 5 years and then be performed every 5 years subsequently. Improving time-of-flight and time-resolved MRA techniques may obviate the need for multiple recurring DSA studies in children after AVM resection, reducing both the cumulative radiation exposure and risk of potential complications from repetitive invasive DSA studies.

The main limitations of our study were the retrospective analysis, single-center, non-randomized study design and the small sample size of pediatric patients with low grade cerebral AVMs. The clinical outcomes were assessed diligently from medical record review, but prone to bias without blinded assessment and documentation errors. This study may be subjected to selection bias for embolization, which is potential for higher complications in the microsurgical only arm. Additionally, possible limitation from tertiary center referral bias that may explain under presentation of infratentorial AVMs in this study [37,38]. Due to the rare incidence of pediatric cerebral low grade AVM, sample sizes in all studies of this pathology remain small and future studies with a larger population would require a multi-institutional cohort or registry.

5. Conclusion

Although microsurgical resection remains the standard treatment of low grade pediatric AVMs, our study demonstrates equivalent safety and favorable clinical outcomes with combined embolization and microsurgical resection treatment in comparison to microsurgical resection alone. In our institutional experience, pre-operative embolization has become an established adjunctive technique that is preferred by our pediatric neurosurgeons for the safe, efficient and complete obliteration of low grade AVMs.

Conflict of interest

The authors have no conflicts of interest or financial relationships to disclose with respect to industry research support, consulting, or speaking.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2019.02.016.

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