



Surgery in Intracerebral Arteriovenous Malformations: The Role of Preoperative Embolization

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<https://turkishneurosurgery.org.tr/uploads/jtn-44032-video2.mp4>

ABSTRACT

AIM: To examine the outcomes of microsurgery only versus combined microsurgery and embolization in treating cerebral arteriovenous malformations (AVM).

MATERIAL and METHODS: A total of 62 patients (34 male and 28 female) with Spetzler–Martin grade 3 (n=44) and grade 4 (n=18) AVMs were examined. Thirty-seven patients were treated with a combination of microsurgery + embolization, whereas 25 patients were treated with microsurgery alone. The clinical characteristics of the treatment groups were compared (ruptured/unruptured, eloquent/non-eloquent, modified Rankin scores, duration of surgery, preoperative and postoperative hemoglobin levels, and use of blood products).

RESULTS: The number of patients with ruptured or eloquently localized AVMs was more in combination of microsurgery + embolization. On the other hand, the duration, preoperative versus postoperative hemoglobin levels, and usage of blood products did not differ between treatment groups.

CONCLUSION: The results of the study showed no superiority of the combined treatment in managing AVMs in parallel to recent meta-analyses. However, a patient-tailored approach is recommended while making the treatment decision for such challenging intracerebral AVM cases.

KEYWORDS: Arteriovenous malformation, Intracerebral, Embolization, Microsurgery

INTRODUCTION

The debate of which treatment methods to follow for AVMs has been going on for years, and there still needs to be a consensus on the best course of action (1,4,9,12,14,16,17,21,24,28). Curative treatment for this condition may include microsurgical resection, endovascular therapy, and stereotactic radiosurgery, which can be used either separately or in combination. The primary objective of these treatment plans is to eradicate the AVM while not increasing the risk any higher than the risk of leaving it untreated. Many

centers use preoperative embolization therapy as an adjunctive treatment method before surgery. The primary goals of this strategy are to reduce intraoperative bleeding and surgery length. Although this treatment strategy is widely used, a comprehensive review of its effectiveness and potential side effects has yet to be conducted (4,6,10,24). Because it is widely acknowledged that preoperative embolization can be harmful and result in stroke, irreversible neurological damage, or even death, there is considerable debate over using this procedure to treat a pathology when it may not even be effective (7,19,22,28). It shall also be considered that embolization

induces significant damage to the blood-brain barrier, neuroinflammation, release of cytokines, and angiogenic growth factors, which may cause harmful remodeling of the AVM microenvironment. These changes may complicate the following surgery and cause AVM recurrence. Indeed, in experimental models of brain ischemia, the cerebral expression of angiogenic Vascular Endothelial Growth Factor (VEGF) increased, and the blood levels of the anti-angiogenic soluble VEGF Receptor-1 (sVEGFR1) decreased (3). In this study, we retrospectively analyzed the cases of AVMs resected microsurgically with or without preoperative embolization in our series. This study aimed to investigate whether preoperative embolization has any additional benefits when used in conjunction with surgical resection of the AVM. First, we document the outcomes of our case series, followed by two cases of AVMs treated with microsurgery alone and with a combined strategy that included preoperative embolization and microsurgery. Their features can be seen in the supplemented video files.

■ MATERIAL and METHODS

Ethical Issues and Design of the Retrospective Study

This retrospective study analyzes 62 AVM patients according to their treatment approach, including those treated with microsurgery alone (n=25) versus those treated with presurgical embolization and microsurgery (n=37) treated between 2015 and 2023. The outcomes of these two groups' treatments were compared. A clinical team led by the study's principal author led all treatment decisions for these patients. All of the individuals studied had AVMs of Grade 3 or 4. Patients who had already undergone stereotactic radiosurgery were not included in the analysis. All the employed procedures were in accordance with the regional and institutional responsible committee's ethical norms, as well as the most recent Helsinki Declaration revisions. The local ethics committee of Memorial Bahcelievler Hospital in Istanbul, Turkey (Approval number: 76; Date: 05.01.2023), granted ethical permission. Informed consent forms were obtained from all the involved patients.

Presurgical Assessments

Neurosurgeons performed neurological examinations using the modified Rankin scale (mRS) at the patients' hospitalization, release, and follow-ups. Each patient had magnetic resonance imaging (MRI) and a digital subtraction angiography (DSA) to highlight the lesions' morphoanatomy and angiographic patterns. In addition, fMRI was performed on patients expected to be involved in the eloquent brain regions. Eloquence was associated with the Wernicke, Broca, and visuosensory and fiber pathways, such as the arcuate fasciculus, pyramidal tracts, and optic radiations. A committed neuroradiologist, a competent neurosurgeon, and one interventional radiologist independently reviewed the neurological imaging. A multidisciplinary approach was used to decide on patient-tailored surgical methods. The following features comprised reasons to perform endovascular microembolization in selected cases: 1—any aneurysm associated with the AVM, 2-dominant feeding arteries of deep origin, 3—a diffuse lesion lacking defined borders, and 4-High-flow fistulous type.

Execution of the Single-Staged Combined Surgery

Endovascular embolizations and surgeries were performed in two separate neighbouring angiography units and operating rooms. Each operating theater was equipped with an operative microscope (Pentero R 900, Carl Zeiss Surgical AG, Oberkochen, Germany), and the angiography unit was outfitted with a multiplanar angiography complex Pheno systems (Siemens Healthineers, Germany). If the embolization and microsurgery procedures were to be performed on the same day, the patient was brought into the operating room after embolization, and the operation began without awakening the patient. Under general anesthesia, the electro-neurophysiological abnormalities were monitored neurophysiologically. Following closure, DSA was used through the guiding catheter to ensure complete lesion occlusion before waking the patient. The microsurgical excision would be repeated until no remaining nidus was found.

Clinical Evaluations and Assessment Criteria

Individual patients' demographic information was recorded, and Spetzler–Martin (S&M) AVM grades were assigned. The modified Rankin scale (mRS) was used to determine the preoperative neurological state. Radiological and physical examinations were performed on the patients. All angiographies and medical data were collected. Furthermore, the surgical times of the two groups (embolization and microsurgery versus microsurgery alone) were compared. The number of blood products and the preoperative and postoperative hemoglobin levels of both groups (embolization and microsurgery versus microsurgery alone) were documented and compared.

Statistical Analysis

All the relevant data were analyzed retrospectively using SPSS software (Version 20.0, IBM, USA). Baseline data were collected quantitatively and qualitatively and compared using normal distribution and non-parametric testing. Quantitative data were presented as mean and standard deviation, whereas qualitative data were presented as percentages. We used Fisher exact and Pearson chi-square analyses to compare results in patients who received microsurgery alone versus combined treatment with microsurgery + embolization. Statistical significance was defined as $p < 0.05$.

■ RESULTS

Table I demonstrates demographical and clinical features of patients. In total, 62 patients (34 men and 28 women) were treated in our institution, with 37 (59.7%) receiving microsurgery and embolization and 25 (40.3%) receiving only microsurgery. There was no statistical difference in treatment strategy between males and females ($p > 0.05$). The median age of patients did not differ based on treatment approach ($p > 0.05$). The combination strategy was used to treat more patients with ruptured AVMs ($p < 0.05$). A greater proportion of patients with eloquent lesion localization (n=20, 55.6%) underwent combination treatment than patients treated with microsurgery alone (n=16, 44.4%). This difference did not reach statistical significance ($p > 0.05$). The percentage

Table I: Demographical and Clinical Features of Patients

Total Number of Patients (n=62)		Embolization+Surgery n=37 (59.7%)	Only Surgery n=25 (40.3%)	p-value
Female	28 (45.2%)	17	11	>0.05
Male	34 (54.8%)	20	14	>0.05
Median Age (year)	27±15.4	28±14.1	21±12.4	>0.05
Ruptured	41	26 (63.4%)	15 (36.6%)	<0.05
Eloquent	36	20 (55.6%)	16 (44.4%)	>0.05
Preoperative mRS Score	1	50	31 (83.8%)	>0.05
	2	6	4 (10.8%)	
	3	3	2 (5.4%)	
	4	2	-	
	5	1	-	

mRS: Modified Rankin Score.

distributions of mRS (modified Rankin scores) did not differ between the two treatment modalities ($p>0.05$).

Table II demonstrates S&M scores of patients. Patients with both S&M 3 (26/44, 59%) and S&M 4 grade (11/18, 61.1%) lesions were more likely to be treated with combination microsurgery + embolization ($p>0.05$). In cases with superficial, deep, and both superficial and deep drainage, more patients underwent combination microsurgery + embolization treatment ($p<0.05$). AVM posterior fossa localization rates did not differ between arms receiving microsurgery and embolization and those receiving microsurgery alone ($p<0.05$). Only patients ($n=9$) who received the combined treatment had an AVM-related aneurysm, whereas none were treated with microsurgery alone. This difference was highly significant ($p=0.00$).

Both treatments were conducted on the same day in 20 of 37 patients who received preoperative embolization with microsurgery and after a 6-week interval in the other 17 patients. A 6-week delay between treatments allows normal perinidal brain tissue adaptation after embolization.

Table III demonstrates the duration of surgical procedures, preoperative and postoperative hemoglobin levels, and blood product usage in two different treatment groups. The numbers regarding blood product usage in Table III represent the total amount of blood units given to the whole group. In the combination therapy arm, embolization lasted 258 ± 35 min. The combination therapy arm and single microsurgery arm had surgery times of 367 ± 44 and 390 ± 41 min, respectively, which did not differ significantly ($p>0.05$). The hemoglobin levels before and after surgery in two distinct treatment groups were not different ($p>0.05$). While 24 units of red blood cell (RBC) suspensions were used in 37 patients who received combined microsurgery and embolization treatment, 16 units of RBC suspensions were used in 25 patients who received only microsurgery (0.65 and 0.64 U/per patient did not differ ($p>0.05$)).

Video Illustrated Cases

Patient 1

The features of the AVM and the methods used on patient 1 can be observed in the supplemented Video File-1. S1. A 28-year-old woman presented with left homonymous hemianopsia and seizure due to a ruptured Grade 4 (S2E1D1) AVM in the right occipital lobe. The AVM was resected using an ipsilateral side down posterior interhemispheric approach. The partial embolization was performed on the day before the surgery. A direct attack was performed from the posterior interhemispheric route, and the main feeder from PCA entering to the calcarine fissure was observed. Embolization was performed with ONYX (Micro Therapeutics, Inc., Irvine, CA). Coils were placed with the request of the surgical team to obtain a guiding point. ICG-VA was obtained before clipping. The dissection of the AVM was completed and total resection was achieved. After resection, ICG-VA was performed again. During the procedure, it was observed that the vein, which is not part of the AVM structure, is preserved during the surgery. A postoperative MRI and DSA confirmed that the AVM had been completely removed. The patient made an excellent recovery and was discharged in a neurologically intact condition.

Patient 2

For the patient-2, the features of the AVM and the applied procedures can be seen in supplemented Video File-2. A 49-year-old woman presented with aphasia and seizures due to a unruptured Grade 4 (S2E1D1) AVM located on the left angular gyrus. A transtemporal approach was used for resecting the AVM. The direct attack was performed from the posterior part of the Sylvian fissure and perinidal dissection was performed and total resection was achieved. This AVM was resected without any preoperative embolization. A postoperative MRI and DSA confirmed complete resection of

Table II: Anatomical Features of AVMs treated with Different Approaches

	Total (n)	Embolization + Surgery (n)	Surgery (n)	p-value
S&M 3	44	26	18	
S3 E0 V0	17	7	10	<0.05
S2 E1 V0	14	10	4	
S2 E0 V1	13	9	4	
S&M 4	18	11	7	
S3 E1 V0	8	3	5	<0.05
S3 E0 V1	6	4	2	
S2 E1 V1	4	4	0	
Only SVD	31	24	7	<0.05
Only DVD	15	11	4	<0.05
Both SVD and DVD	16	14	2	<0.05
Posterior fossa localization	9	5	4	>0.05
AVM-related aneurysm	9	9	0	=0.00

S&M: Spetzler Martin grade, **S:** Size, **E:** Eloquency, **V:** Venous drainage, **SVD:** Superficial venous drainage, **DVD:** Deep venous drainage, **AVM:** Arteriovenous malformation.

Table III: Durations of Surgery, Hemoglobin Levels, Usage of Blood Products

	Duration of the Surgical Intervention (minutes) (mean ± standard deviation)	Preoperative Hemoglobin (gr/dL) (mean ± standard deviation)	Postoperative Hemoglobin (gr/dL) (mean ± standard deviation)	Blood Product Use*
Embolization+Surgery	367 ± 44	11.1 ± 1.2	10.3 ± 1.6	24 units of RBC in 37 patients
Surgery alone	390 ± 41	11.9 ± 1.4	10.4 ± 1.1	16 units of RBC in 25 patients
p-value	>0.05	>0.05	>0.05	>0.05

*The numbers regarding blood product usage in Table III represent the total amount of blood units given to the whole group.

the AVM. The patient made an excellent recovery and was discharged in a neurologically intact condition.

■ DISCUSSION

A randomized unruptured brain (ARUBA) trial was conducted to reveal the best treatment for the unruptured brain AVMs, demonstrating that conservative treatment is superior to surgical intervention (17). Nonetheless, this study has received widespread criticism for poor patient allocation and selection bias, short follow-up, and use of nonstandard care (11,12,15,18,24). Preoperative AVM embolization is commonly used as an adjuvant to surgery to make excision safer by decreasing AVM size, nidus blood flow, and other high-risk features. According to certain researchers, presurgical embolization can expand the number of operable AVMs that can be used in single or multiple sessions depending on the architectural complexity of the nidus (6). Despite the proposed hypothetical benefits of presurgical embolization, such as reduced hemorrhage and surgical time, insufficient data support its routine utilization. Nonetheless, this practice harbors risks of serious complications, including stroke, neurological disability, and even mortality (4). Further, despite the latest improvements in endovascular implementations, embolization of AVMs is still highly challenging, especially for those having plexiform structure, distantly localized nidus, and tiny tortuous arterial feeders to approach (8). The morbidity and mortality risks of any treatment are acceptable only if matched or exceeded by the AVM's latter risk of bleeding. Multimodality treatment may also result in the accumulation of risks from the

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various treatments (28). Furthermore, there is no exact measure of what is beneficial to surgery.

In our current study, more AVM patients were treated with a combined approach that included embolization and microsurgery. Nonetheless, this was not related to the physio-anatomy of the lesions. This fact was related to our earlier acceptance that a combined approach in AVM treatment would provide better clinical outcomes than microsurgery alone. The only slight difference regarding that a higher number of AVM patients with eloquent localization were treated with combined treatment was due to our still ongoing intention in a few selected cases. Because of their nidus size and the presence of deep venous drainage, eloquently situated AVMs may be associated with increased surgical risks. Hence, eloquent localization may be one of the factors which may be regarded as a reason to use combined embolization and microsurgery in a patient-tailored approach.

When the two cases discussed above are reviewed, two AVMs of the same grade (ruptured and nonruptured) are observed. In both cases, the operative times are very close to each other. In both cases, the amount of bleeding during the surgery is very close. In either case, no blood transfusion was required. When we describe our experience during surgery, the need to use clips was absolute in the first case due to preoperative embolization. According to our estimates, because preoperative embolization was incomplete, the blood flow that fed the AVM was redistributed, making coagulation with bipolar alone challenging, particularly in the non-embolized regions. In the second case, although it was not preoperatively embolized, even if a temporary clip was placed, only bipolar coagulation was more comfortable, and the temporary clip was removed later due to a calmer AVM and surrounding tissue. Permanent clip application in AVM surgery may indicate that it is an indirect but healthy indicator of how difficult hemostasis can be. Therefore, preoperative embolization, while not strictly a rule, can make AVM surgery a more challenging procedure. This interpretation should not imply that embolization should never be performed. However, it can be concluded that early surgery after embolization is more challenging than late surgery if the AVM is partially closed by embolization. For this reason, it may be preferable to plan surgical removal at least 6–8 weeks after the embolization intervention or not to perform preoperative embolization in the surgical planning of AVMs that are unlikely to be fully embolized. Of course, it should be noted that an AVM that has not been fully treated during this 6–8-week period may increase the risk of bleeding.

Complications of presurgical embolization can happen due to intraprocedural technical complications or alterations in flow hemodynamics. The pathophysiology of flow-related bleeding is considered to occur due to the rupture of dysautoregulated blood vessels surrounding the AVM, which experience a pressure increase during the reversal of arteriovenous shunts or as a result of a residual nidus. Because of the unavoidable formation of cortical transmedullary and transdural collaterals, proximal occlusion of arterial feeding vessels and lack of success in clogging the nidus with embolic material may have a nega-

tive impact on the procedure (22). If a significantly contributing deep perforating artery cannot be effectively embolized, surgical bleeding risk is high regardless of the embolization efficacy of non-perforating arteries (20). Furthermore, surgical complications may be increased if embolization results in a compensatory increase in diameter or flow of unembolized feeding arteries, which contain a deep thin-walled perforator component (20). Moreover, overembolization of AVM feeding arteries might result in hypertrophy of deep white matter feeders, increasing the technical complexity of microsurgery (7).

Subat et al. conducted a meta-analysis to reveal the pooled rates of flow-related and total periprocedural bleeding after AVM embolization, bleeding-associated morbidity and mortality, and risk factors for this complication (27). Their analysis revealed a pooled total bleeding rate per procedure of 1.8% for adjuvant (surgery or radiosurgery) and 4.6% for curative intent. The importance of periprocedural bleeding is revealed by its morbidity and mortality rates—45.1% and 14.6%, respectively—and the rates were similar regardless of the bleeding etiology (flow-related or technical). Furthermore, pooled ischemia rates were found for 2.4% per procedure and 4.5% per patient (27). Hartmann et al. analyzed 119 patients with brain AVMs treated with endovascular embolization and subsequently with surgical treatment (13). Disabling and nondisabling treatment-related complications occurred in 5% and 42% of the patients, respectively, with no treatment-related deaths. Large AVM size, presentation without bleeding, deep venous drainage, and location in the eloquent brain were all independent determinants of the new treatment-associated deficits (13). Morgan et al. reported that they discontinued using the embolization for S&M Grade 1 and 2 AVMs because the sum of risks for both approaches was higher than the risk associated with surgery alone (19).

In the largest case series ever reported, Donzelli et al. evaluated their cohort of 319 AVM patients operated by a single neurosurgeon and analyzed whether subjects with and without embolization differed with respect to patient and AVM characteristics (10). Embolized AVMs were larger and less likely to have hemorrhaged, or diffuse. Further, embolized AVMs tended to have both superficial and deep venous drainage and were less likely to harbor exclusive deep drainage. In multivariable statistical analysis, embolization did not correlate with blood loss or mRS score changes and was even associated with longer operating times and higher numbers of clip usage (10). Another issue is that the angiography may overestimate embolization success since residual fillings were found in AVMs with angiographically demonstrated obliteration. Additionally, recanalizations may occur after AVM embolization, and both recanalizations and residual fillings resulting from incomplete lesion operation may paradoxically increase the risk of hemorrhage relative to microsurgery alone (24). A further concern regarding embolization is the heterogeneous nature of the embolization materials (10). Squid, ONYX, and PHIL, as well as their subtypes, are the most often used liquid embolization agents (LEAs). LEAs' low viscosity may result in less effective proximal plugs, accidental embolization of non-target arteries, which supply healthy brain tissue, and early distal embolization occluding draining veins (30). Moreover, all

the LEAs mentioned above might cause proinflammatory and vasotoxic effects. For the cyanoacrylates, the toxicity is higher and associated with releasing highly toxic formaldehyde and acryl acetate (2,30).

In addition to discussing whether embolization should be performed before AVM surgeries, another important discussion is about the exact time when embolization will be performed before surgery. Surgery may become an urgent necessity when embolization issues arise, such as bleeding or the catheter attached to the AVM nidus. The sudden change in the tissue around the AVM due to the sudden decrease or interruption of the flow after embolization also increases the risk of surgery immediately after embolization. Vinuela et al. shared their experience with the presurgical embolization of 465 AVM cases (29). In their general practice, they preferred a staged embolization with an interval between microembolization and surgical excision of the residual nidus between 7 to 14 days. But, surgical resection of the residual AVM was performed only as an emergency procedure only if there was angiographic evidence of stagnation in the dominant AVM draining veins. They conclude that staged presurgical embolization of AVMs within 1–2 weeks before surgery is a plausible approach (29).

Spetzler et al. reported 20 giant AVM cases of Grade-4 according to S&M classification, located adjacent to or within the eloquent brain (26). In all these cases, they performed presurgical embolization, and if the embolization was complete, the feeding artery was generally ligated at the site of cannulation. This procedure hindered the increased proximal pressure associated with embolization from being transmitted to residual nonoccluded nidal segments supplied by the feeding artery (26). This approach resulted in full excision in 18 (90%) of patients, with no deaths and only three complications, of which one was disabling. Spetzler et al. concluded that the immediate presurgical embolization rendered AVMs, which were considered inoperable or marginally operable, into completely excisable lesions. In addition, this immediately staged combined approach provided acceptable morbidity and mortality rates (26).

Wang et al. published their treatment results regarding AVMs, which are adjacent to or within the eloquent brain, using the single-staged approach with immediate presurgical microembolization (31). They stated that the reason for selecting such an approach is related to insufficient lesion-to-eloquence distance (LED), which causes poor neurological outcomes after surgery. After partial embolization of the nidus adjacent or within the eloquent areas, the rest was surgically excised during the same procedure in 9 patients. Importantly, all treated cases achieved total AVM obliteration without complications or neurological complications (31). The authors concluded that such a single-staged *in situ* approach may have helped reduce the nidal blood flow after surgery, providing fast quality checks with post-excision intraoperative angiograms and immediate observation of AVM occlusion and increasing the LED to avoid eloquent areas from being injured. Further, such an approach provided a bloodless surgical plane hindering the sacrificing of the parenchyma for hemostasis. Finally, embolic agents acted as arterial feeder markers preventing negligent injury to adjacent arteries (31).

Brown et al. reported that the bleeding risk from preoperative AVM embolization is 11%, with 52% occurring due to non-arterial perforation (5). Eighty-one percent of these bleedings occur within 34.4 h post embolization. Hence, Brown et al. proposed that the bleeding risk could be avoided by employing microsurgical resection on the same day of embolization (5). However, the authors did not address the surgical difficulties when the embolization is performed on the same day of AVM surgery. In a prospective multicenter study, Zeng et al. defined the combination of presurgical embolization with microsurgery as hybrid surgery and compared the outcomes of single-staged hybrid surgery (SSHS) with the outcomes of multi-staged hybrid surgery (MSHS) (32). There were no statistically significant differences in the clinical features and demographics between these groups. Seven ruptures occurred in the interval between microembolization and microsurgery for the MSHS group versus none in the SSHS group, resulting in a rupture risk of 4.1% per year for the MSHS group (32). The authors found that with similar rates of AVM occlusion, reduced interval bleeding and surgical risks can be obtained with single-stage surgery, even in complex intracranial AVMs (32).

Intracranial AVMs are uncommon in children, accounting for 3%–20% of all AVMs, but they produce 30%–50% of spontaneous intracranial hemorrhage in the pediatric population, resulting in significant morbidity and mortality rates (25). Soltanolkotabi et al. reported 25 pediatric cases requiring 38 endovascular embolization procedures to occlude 56 pedicles (25). Ten complications (26.3%) were encountered in 38 procedures; among those, 4 were transient neurological, 4 were transient nonneurological complication, and the remaining were clinically silent. Only deep venous drainage was found to be a risk factor for increased complication rates. The authors underlined that all the witnessed complications were either transient or silent; however, they also noted that the overall rate of complications was higher than their expectation (25). Pepper et al. reviewed 50 children with a mean follow-up of 7.6 years; among those, 40 (80%) presented with hemorrhage on initial imaging (23). The AVM drainage was superficial in 51% of cases, and the lesions were localized in the eloquent cortex in 56%. Their S&M grades were Grade 4 and above in 78% of cases. Primary treatment approaches included embolization in 50%, SRS in 30% and surgery in 20%. Three children had postprocedural bleeding, two associated with embolization and one the day after SRS, with a rebleed rate of 6%. There were two mortalities due to acute bleeding (4%). The authors reported that most children patients with AVM present with bleeding and also that the judicious utilization of these 3 diverse treatment approaches widely reduced mortality and serious disability (23). To our view, especially in pediatric low-grade AVMs (Grade 1 and Grade 2), clinicians should not even consider preoperative embolization, since these AVMs already constitute the lowest surgical risk group. Hence, there is no point in adding a further risk of endovascular embolization. Furthermore, according to our clinical experience, it would be more appropriate to plan surgical treatment without preoperative embolization in high-grade pediatric AVMs suitable for surgery.

In 2022, two meta-analysis and review studies from the Johns Hopkins University (USA) and Trinity College (Ireland) were published comparing clinical outcomes of combined microsurgery and embolization with single microsurgery in the management of AVMs (4,24). The study of Sattari et al. revealed that obliteration of AVMs, morbidity, and mortality rates were similar in the combined approach and microsurgery alone (24). While the meta-analysis of Sattari et al demonstrated that the combined treatment and single microsurgery strategies are similar, the authors questioned whether these findings may be influenced by selection bias, in which more complex lesions were treated with embolization. Despite this, their subgroup analysis of the S&M 3–4 lesion group showed increased obliteration rates after microsurgery versus the combined approach, indicating that the selection bias may not influence the obtained data. The authors also mentioned that microsurgical obliteration rates were very high (90% and 100% for ruptured and unruptured lesions, respectively) in low-grade AVMs, further indicating that the presurgical embolization does not add additional clinical benefit. Brosnan et al. performed a MEDLINE search, and according to the Cochrane Handbook and PRISMA guidelines, they analyzed articles reporting outcomes of presurgical AVM embolizations (4). Their primary outcome assessment was the complication risks associated with presurgical embolization. The analysis of 1,661 citations and 588 patients from eight eligible studies revealed that there is no sufficient evidence to advise presurgical AVM embolization (4).

S&M Grade 3 and Grade 4 AVMs are not homogeneous. Each AVM case should be evaluated individually and regardless of S&M Grade (except Grade Vs), if possible, as a one-time surgical intervention in treatment planning. For example, if AVMs located in the caudate nucleus and thalamus localizations get one score each from the points of localization in the eloquent area and have deep venous drainage, an AVM with a nidus diameter of 1 cm will be Grade 3. An AVM with a nidus diameter greater than 6 cm in localization, such as the right frontal lobe and right temporal lobe, will also be at least Grade 3. Therefore, if they are based on localization rather than the diameter of the lesion, SRS should be considered in the first line of treatment.

Limitations of the Study

One of the main drawbacks of this study is that the results are based on the experience of a single neurosurgeon. A randomized, double-blind prospective multicenter study should be conducted to reach a more descriptive result. Another limitation of the study is that it is retrospective, with a small number of patients included. We have not randomized the patients even though the baseline characteristics were similar in the two groups. As these results are informative, the focus of this work merits more extensive prospective randomized trials investigating the above-mentioned subject.

CONCLUSION

Our findings are consistent with other studies and meta-analyses which showed lack of superiority of the combined endovascular embolization and microsurgery approach to

microsurgery alone in treating cerebral AVMs. Based on these observations and according to our clinical findings declared above, we advocate the microsurgical approach alone in treating AVMs if there is no significant contraindication for surgery in the individual patient.

AUTHORSHIP CONTRIBUTION

Study conception and design: MB

Data collection: MO, KE

Analysis and interpretation of results: MO, KE

Draft manuscript preparation: MO

Critical revision of the article: MB

Other (study supervision, fundings, materials, etc...): MB

All authors (MO, KE, MB) reviewed the results and approved the final version of the manuscript.

REFERENCES

1. Al-Shahi R, Warlow C: A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. *Brain* 124:1900-1926, 2001
2. Bakar B, Oruckaptan HH, Hazer BD, Saatci I, Atilla P, Kilic K, Muftuoglu SF: Evaluation of the toxicity of onyx compared with n-butyl 2-cyanoacrylate in the subarachnoid space of a rabbit model: An experimental research. *Neuroradiology* 52(2):125-134, 2010
3. Bayraktar B, Turkoz D, Turkoz A, Karkucak A: Effects of cerebral ischemia on levels of vascular endothelial growth factor (VEGF) and its soluble receptors: A possible link to angiogenesis in arteriovenous malformations. *Turk Neurosurg* 31:907-912, 2021
4. Brosnan C, Amoo M, Javadpour M: Preoperative embolisation of brain arteriovenous malformations: A systematic review and meta-analysis. *Neurosurg Rev* 45(3):2051-2063, 2022
5. Brown D, Graham C, Smith A, Storey M, Robson C, Maliakal P, Kounin G, Castanho P: Same day embolisation followed by microsurgical resection of brain arteriovenous malformations: A single centre early experience. *Br J Neurosurg* 35(1):80-83, 2021
6. Chen CJ, Ding D, Derdeyn CP, Lanzino G, Friedlander RM, Southerland AM, Lawton MT, Sheehan JP: Brain arteriovenous malformations: A review of natural history, pathobiology, and interventions. *Neurology* 95:917-927, 2020
7. Conger A, Kulwin C, Lawton MT, Cohen-Gadol AA: Diagnosis and evaluation of intracranial arteriovenous malformations. *Surg Neurol Int* 6:76, 2015
8. Deniwar MA, Mustafa W, Elfeki H, Eldin AE, Awad BI: Transvenous embolization of brain arteriovenous malformations: Up-to-date meta-analysis. *Turk Neurosurg* 32:525-534, 2022
9. Derdeyn CP, Zipfel GJ, Albuquerque FC, Cooke DL, Feldmann E, Sheehan JP, Torner JC; American Heart Association Stroke Council: Management of brain arteriovenous malformations: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 48:e200-e224, 2017

10. Donzelli GF, Nelson J, McCoy D, McCulloch CE, Hetts SW, Amans MR, Dowd CF, Halbach VV, Higashida RT, Lawton MT, Kim H, Cooke DL: The effect of preoperative embolization and flow dynamics on resection of brain arteriovenous malformations. The effect of preoperative embolization and flow dynamics on resection of brain arteriovenous malformations. *J Neurosurg* 132:1836-1844, 2019
11. Elhamady MS, Heros RC: Editorial: The ARUBA study: Where do we go from here? *J Neurosurg* 126:481-485, 2017
12. Feghali J, Huang J: Updates in arteriovenous malformation management: the post-ARUBA era. *Stroke Vasc Neurol* 5:34-39, 2019
13. Hartmann A, Mast H, Mohr JP, Pile-Spellman J, Connolly ES, Sciacca RR, Khaw A, Stapf C: Determinants of staged endovascular and surgical treatment outcome of brain arteriovenous malformations. *Stroke* 36:2431-2435, 2005
14. Kocer N, Kandemirli SG, Dashti R, Kizilkilic O, Hanimoglu H, Sanus GZ, Tunali Y, Tureci E, Islak C, Kaynar MY: Single-stage planning for total cure of grade III-V brain arteriovenous malformations by embolization alone or in combination with microsurgical resection. *Neuroradiology* 61:195-205, 2019
15. Lawton MT, Lang MJ: The future of open vascular neurosurgery: Perspectives on cavernous malformations, AVMs, and bypasses for complex aneurysms. *J Neurosurg* 130:1409-1425, 2019
16. Liu R, Zhan Y, Piao J, Yang Z, Wei Y, Liu P, Chen X, Jiang Y: Treatments of unruptured brain arteriovenous malformations: A systematic review and meta-analysis. *Medicine (Baltimore)* 100(25):e26352, 2021
17. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, Al-Shahi Salman R, Vicaud E, Young WL, Houdart E, Cordonnier C, Stefani MA, Hartmann A, von Kummer R, Biondi A, Berkefeld J, Klijn CJ, Harkness K, Libman R, Barreau X, Moskowitz AJ; international ARUBA investigators. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): A multicentre, non-blinded, randomised trial. *Lancet* 383:614-621, 2014
18. Moon K, Levitt MR, Almefty RO, Nakaji P, Albuquerque FC, Zabramski JM, Wanebo JE, McDougall CG, Spetzler RF: Safety and efficacy of surgical resection of unruptured low-grade arteriovenous malformations from the modern decade. *Neurosurgery* 77:948-952, 2015
19. Morgan MK, Davidson AS, Koustais S, Simons M, Ritson EA: The failure of preoperative ethylene-vinyl alcohol copolymer embolization to improve outcomes in arteriovenous malformation management: Case series. *J Neurosurg* 118: 969-977, 2013
20. Morgan MK, Zurin AA, Harrington T, Little N: Changing role for preoperative embolisation in the management of arteriovenous malformations of the brain. *J Clin Neurosci* 7:527-530, 2000
21. Nerva JD, Mantovani A, Barber J, Kim LJ, Rockhill JK, Hallam DK, Ghodke BV, Sekhar LN: Treatment outcomes of unruptured arteriovenous malformations with a subgroup analysis of ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations)-eligible patients. *Neurosurgery* 76:563-570, 2015
22. Ogilvy CS, Stieg PE, Awad I, Brown RD Jr, Kondziolka D, Rosenwasser R, Young WL, Hademenos G; Stroke Council, American Stroke Association. Recommendations for the management of intracranial arteriovenous malformations: A statement for healthcare professionals from a special writing group of the Stroke Council, American Stroke Association. *Circulation* 103:2644-2657, 2001
23. Pepper J, Lamin S, Thomas A, Walsh AR, Rodrigues D, Lo WB, Solanki GA: Clinical features and outcome in pediatric arteriovenous malformation: Institutional multimodality treatment. *Childs Nerv Syst* 39(4):975-982, 2023
24. Sattari SA, Shahbandi A, Yang W, Feghali J, Xu R, Huang J: Microsurgery versus microsurgery with preoperative embolization for brain arteriovenous malformation treatment: A systematic review and meta-analysis. *Neurosurgery* 92:27-41, 2023
25. Soltanolkotabi M, Schoeneman SE, Alden TD, Hurley MC, Ansari SA, DiPatri AJ Jr, Tomita T, Shaibani A: Onyx embolization of intracranial arteriovenous malformations in pediatric patients. *J Neurosurg Pediatr* 11:431-437, 2013
26. Spetzler RF, Martin NA, Carter LP, Flom RA, Raudzens PA, Wilkinson E: Surgical management of large AVM's by staged embolization and operative excision. *J Neurosurg* 67:17-28, 1987
27. Subat YW, Dasenbrock HH, Gross BA, Patel NJ, Frerichs KU, Du R, Aziz-Sultan MA: Periprocedural intracranial hemorrhage after embolization of cerebral arteriovenous malformations: A meta-analysis. *J Neurosurg*, 2019 (Online ahead of print)
28. van Beijnum J, van der Worp HB, Buis DR, Al-Shahi Salman R, Kappelle LJ, Rinkel GJ, van der Sprenkel JW, Vandertop WP, Algra A, Klijn CJ: Treatment of brain arteriovenous malformations: A systematic review and meta-analysis. *JAMA* 306:2011-2019, 2011
29. Vinuela F, Duckwiler G, Guglielmi G: Contribution of interventional neuroradiology in the therapeutic management of brain arteriovenous malformations. *J Stroke Cerebrovasc Dis* 6:268-271, 1997
30. Vollherbst DF, Chapot R, Bendszus M, Möhlenbruch MA: Glue, Onyx, Squid or PHIL? Liquid embolic agents for the embolization of cerebral arteriovenous malformations and dural arteriovenous fistulas. *Clin Neuroradiol* 32:25-38, 2022
31. Wang M, Qiu H, Cao Y, Wang S, Zhao J: One-staged in situ embolization combined with surgical resection for eloquence protection of AVM: Technical note. *Neurosurg Rev* 42:783-790, 2019
32. Zeng C, Wang M, Song X, Zhang C, Lin F, He Q, Yang W, Cao Y, Wang S, Tu W, Zhao J: Multimodal treatments of brain arteriovenous malformations: A comparison of microsurgical timings after endovascular embolization. *Ann Transl Med* 10: 732, 2022