Arquivos Médicos
DOS HOSPITAIS E DA FACULDADE DE CIÊNCIAS MÉDICAS DA SANTA CASA DE SÃO PAULO

REVIEW

Arq Med Hosp Fac Cienc Med Santa Casa São Paulo. 2021; 66:e003
https://doi.org/10.26432/1809-3019.2021.66.003

Multimodal treatment of brain arteriovenous malformations: microsurgery, radiosurgery and endovascular

Tratamento multimodal das malformações arteriovenosas cerebrais: microcirurgia, radiocirurgia e endovascular

Márcio Alexandre Teixeira Costa [1], Mario Luiz Marques Conti [1], Aline Lariessy Campos Paiva [1], José Carlos Esteves Veiga [1], Guilherme Brasileiro de Aguiar [1]

Abstract

Introduction: *Arteriovenous malformations (AVMs) are abnormal communications between artery and veins without capillary interconnections. Because of this flow alteration, they can easily rupture and bleeding could be catastrophic. Diagnosis is performed through neuroimaging methods. Then, careful evaluation is required in deciding for the best treatment approach: microsurgery, radiosurgery or endovascular.* ***Objective***: *This paper aims to describe the main indications, advantages and disadvantages of each method.* ***Methods***: *A PubMed database literature review was performed. The following English language keywords were used: "brain AVM", "arteriovenous malformations", "radiosurgery", "microsurgery", "embolization" and "endovascular". Recent high impact factor papers were selected for this review.* ***Discussion***: *The Spetzler-Martin classification is indispensable for prognosis acknowledgment and for the proper therapeutic approach selection, however is not sufficient for decision-making. Other factors, such as the patient's general clinical condition, surgeons experience and availability of all of the treatment methods are essential. Microsurgery is the gold standard method for treatment of AVM's, however, more and more, less invasive methods, such as radiosurgery and endovascular, are expanding. In some cases, they could be used as single treatment, nevertheless they act as adjuvants to microsurgery.* ***Conclusions***: *The knowledge of the advantages, disadvantages and limitations of each technique allow for a better decision, aiming for a greater cure rate and less morbidity. Combined surgical and radiosurgery approaches, embolization and surgical or embolization and radiosurgery are increasingly being used to improve occlusion rates with fewer neurological deficits.*

Keywords: *Arteriovenous malformations, Neurosurgical procedures, Radiotherapy, Endovascular procedures, Combined modality therapy*

Resumo

Introdução: *As malformações arteriovenosas (MAVs) são comunicações anormais entre artérias e veias, sem a interposição de capilares. Devido a esta troca de fluxo, são propensas a rotura e sangramento, que podem ser catastróficos. Seu diagnóstico é realizado através de métodos de neuroimagem. Após o diagnóstico é necessária cuidadosa avaliação de diversos fatores para decidir sobre o melhor tratamento a ser instituído: microcirurgia, radiocirurgia ou embolização endovascular.* ***Objetivo***: *Este estudo tem objetivo de descrever as principais indicações, vantagens e desvantagens de cada método.* ***Métodos***: *Revisão da literatura utilizando a base de dados Pubmed, considerando como palavras-chave na língua inglesa: "brain AVM", "arteriovenous malformations", "radiosurgery", "microsurgery", "embolization" and "endovascular".* ***Discussão***: *A utilização da classificação de Spetzler-Martin é indispensável para o correto planejamento terapêuticos das MAVs. No entanto, somente isso não é suficiente para a melhor tomada de decisão. Fatores como estado geral do paciente, disponibilidade de todas as modalidades terapêuticas e experiência do cirurgião são essenciais. A microcirurgia é o método consagrado para o tratamento, mas os métodos menos invasivos, como a radiocirurgia e a embolização endovascular, têm ganhado cada vez mais espaço, tanto como modalidade única, ou como tratamento adjuvante à cirurgia, em casos selecionados.* ***Conclusões***: *O conhecimento das vantagens, desvantagens e limitações de cada técnica propicia a escolha da melhor modalidade terapêutica, objetivando maiores índices de cura e menor morbimortalidade. Cada vez mais o tratamento combinado, seja radiocirurgia com microcirurgia ou embolização com microcirurgia, vem sendo utilizado para maximizar as taxas de oclusões completas, com menos sequelas neurológicas.*

Palavras Chave: *Malformação arteriovenosa, Proce-*

1. Santa Casa de Sao Paulo School of Medical Sciences. Department of Surgery. São Paulo – SP – Brazil
Institution: *Santa Casa de Sao Paulo School of Medical Sciences. Department of Surgery. São Paulo – SP – Brazil*
Correspondence address: *Guilherme Brasileiro de Aguiar. Rua Mato Grosso, 306 – Conj. 404 – Higienópolis – 01239- 040 - São Paulo – SP- Brasil. E-mail: guilhermebraguiar@yahoo.com.br*

dimentos neurocirúrgicos, Radioterapia, Procedimentos endovasculares, Terapia combinada

Introduction

Brain arteriovenous malformations (AVMs) are congenital blood vessel anomalies derived from capillary network maldevelopments allowing direct connections between cerebral arteries and veins[1]. These lesions can be asymptomatic, however more frequently they present as brain hemorrhages, especially in young patients without previous arterial hypertension history. Sometimes they cause compressive neurological deficits effects such as hemiparesis. In other cases, epileptic seizures.

The annual cerebral arteriovenous malformation hemorrhage risk is approximately 3%, but depending on the clinical and anatomical malformation features, the risk may be higher[1]. A ruptured AVM has a higher risk of a new rupture occurrence when compared to a non-ruptured AVM. Approximately 4,5% - 34% for the first rupture and from 0,9%-8% for the second rupture[2-4]. They represent the causes of 2% of all strokes and 38% of all intracerebral hemorrhages in patients between 15 and 45 years of age[2-3].

Its etiology is not well known and its behavior sometimes is surprising. AVM's are thought to be congenital in nature because they lack intervening capillary beds[3]. They could be described as lesions with a congenital persistence of very primitive arteriovenous shunts that should have been replaced by normal intervening capillaries during the first 3 months of embryogenesis[5]. Despite this congenital etiology theory, many times they only have neurological manifestations during adulthood. During childhood, the hemodynamic alterations are compensated, so bleeding is even rarer.

Diagnosis is performed through cerebral angiography and/or magnetic resonance imaging (MRI). Both methods are required for a proper evaluation, classification and prognosis assessment. Natural history is not well known and some AVMs never develop ruptures, generally some type of a therapeutic intervention is proposed. Many factors must be considered for this decision and they will be listed as following.

The gold standard and definitive treatment for cerebral arteriovenous malformations is complete microsurgical removal by an experienced neurosurgeon [6]. Nowadays there are other options, basically one of the four approaches: conservative, microsurgery, radiosurgery or endovascular treatment. Gamma Knife (GK) is a well stablished method specially for small deep-located lesions. Embolization as single treatment is used in selected cases, however, more frequently is associated to surgery or radiosurgery.

The knowledge of the various techniques that can be used in the treatment of AVMs must be widely disseminated among professionals who deal with this disease. Thus, the mainly indications, limitations, advantages and disadvantages of these methods will be discussed in this review.

Methods

A literature review using Pubmed database was performed considering terms in English: "brain AVM", "arteriovenous malformations", "radiosurgery", "microsurgery", "embolization", "endovascular treatment". The most recent and relevant papers were selected and analyzed for performing this review. A case treated by the authors is presented.

As there is no identification of patient or inclusion of medical record data, written patient consent or approval of Institution's Ethics Board in these situations are waived.

Discussion

Arteriovenous malformations (AVMs) are cerebrovascular abnormalities that have fistulous connections of arteries to veins with no normal intervening capillary beds [3]. They have interposed cerebral tissue unlike the cavernous angioma. Another difference among these two types of malformations is that AVMs appear in angiography, and, on the other hand, cavernous angiomas are angiographically occult.

AVMs tend to be triangular with the base at the meninges and the apex located toward the ventricles. Among vascular malformations, considering cavernomas and fistulas, AVMs are the most frequently detected symptomatic vascular malformations. They represent the cause of 2% of all strokes and 38% of all intracerebral hemorrhage in patients between 15 and 45 years of age[1]. Progressive neurologic deficits can also occur as an initial manifestation, as well as epilepsy. Because of its complex anatomy, hemodynamic alterations lead to an increased bleeding risk, specially the huge and deep-located AVMs.

Ruptured AVMs have a high annual risk of repeat hemorrhage (4.5%–34%)[4]. Because of this, treatment selection must consider induced hemodynamic changes. Also, if the malformation is located deep within the brain or brain stem or is characterized by exclusively deep venous drainage[7]. Intranidal aneurysms and fistulas associated to the AVM are not uncommon. They increase the rupture risk and must be considered during the decision-making process of treatment. Sometimes the hemorrhage is due to aneurysm rupture and not because of the AVM. Restriction of venous drainage occurs from narrowing or occlusion of one or more of the main draining veins of the arteriovenous malformation. Consequently, venous outflow restriction is associated with the highest risk when the malformation has only a single draining vein.

It can be noticed that there are several factors that should be considered for deciding the best therapeutic approach [8]. Therefore, classifying AVMs could help for this decision, make feasible the discussion among several specialized centers and give prognosis information.

The most used and popularized classification is the Spetzler-Martin grading scale [9]. It was originally developed to predict the outcome of microsurgical treatments but can also be used to predict the radiosurgical outcome. The five-grade scale incorporates points for three features of the arteriovenous malformation: the diameter (<3 cm [1 point], 3 to 6 cm [2 points], or >6 cm [3 points]), presence of deep venous drainage (1 point), and involvement of an eloquent location (1 point). Lower grades (lower total points) indicate lower risk of treatment. An even more accurate prediction of the radiosurgical outcome has been achieved with the Virginia Radiosurgery AVM Scale (VRAS) [10-11]. The VRAS assigns one of five grades on the basis of points for volume size, eloquent location, and history of cerebral hemorrhage. Grade 1 arteriovenous malformations have 0 points, and grade 5 malformations have 4 points.

Nowadays, 90 years after the first comprehensive surgical status report for AVMs published in 1928 by Dandy[12], and after the first report of a complete AVM excision treatment performed by combined surgery and radiotherapy by Cushing[13], AVMs natural history, the best treatment option and when to treat the AVM, still remains a polemic theme.There are some relevant trials that deserve to be highlighted designed to guide decision-making, however their conclusions could not be accepted without an individualized discussion.

In 2014, the published study of "Medical management with or without interventional therapy for unruptured brain arteriovenous malformations" (ARUBA), a randomized trial, compares interventional therapy and medical management of unruptured brain arteriovenous malformations (uBAVMs)[14]. This study concludes that the natural history of uBAVMs is better than any other form of treatment. However, this trial was criticized for this result. The main criticisms relate to the wide heterogeneity of treatment modalities, the absence of subgroup analyses, the lack of details on the results of specific treatments, an insufficient follow-up period, a small patient population, and the bias related to the high-stakes and irreversible consequences influencing the decision to be randomized.

In despite, the ARUBA study is a respected publication. Neurosurgeons did not systematically change their decisions and conservative treatment is an exception. Some researchers defend stopping all types of treatments[15]. Nevertheless, the question that must be made is the following: is it worth it? If the exact natural history is not known is it worth just to wait and see?

Another trial that intended to study AVMs better was the treatment of brain AVMs study (TOBAS). It was a randomized care trial (RCT)[4]. Patients are offered two options with equal chances of being selected: 50% of chance in getting the intervention and a 50% of chance in being managed according to the previously validated treatment (observation when none exists). TOBAS did not include any selection criteria, and an algorithmic decision-making process that, at the time of a multidisciplinary meeting, combines clinical judgment and pre-randomization to facilitate the participation of clinicians and patients in the randomized portions of the study. All patients with bAVMs presenting to participating centers were included. Because patients with Spetzler-Martin 1 and 5, for example, are included at the same sample it is possible to notice that some bias occurred. Also, it is necessary to include a greater number of participating centers for a better understanding.

After discussing the main topics about AVMs it is possible to highlight important features related to treatment options. Basically, four types can be proposed: conservative, microsurgery, radiosurgery and endovascular. Notwithstanding, conservative treatments should be reserved for special cases such as for very small lesions, very huge lesions that are inoperable and also for the radiosurgical or endovascular approach that could not be enough for obliteration, as defended by the ARUBA study. Watch and see a disease that does not have a well-stablished natural history could be fatal and risky. A proper dialogue between the physician and patient should be held.

Radiosurgery

Stereotactic radiosurgery (SRS), specially with the use of the Gamma Knife (GK), is an effective treatment option for the management of brain arteriovenous malformations [16,17], and is particularly effective for small-to medium-sized nidi located in deep or eloquent brain regions that have difficult microsurgical accesses, for example, the thalamus. Careful surgical planning using MRI and angiography must consider vein drainage in respect to post-operative venous congestion.

Since hemodynamic changes do not occur immediately and since it is not so predictable as in microsurgery, special care is necessary in the first weeks and months after the procedure. Bleeding can occur before nidus occlusion. This is relevant in huge AVMs, and one of the reasons is that they should not be only treated with SRS. In addition to the obstructive effect being less in high doses.

Thus, the complications of SRS should be known. The earliest and most frequently observed complication after SRS for AVMs is radiation-induced changes (RICs), which typically manifests 6 to 18 months after as perinidal T2 signal changes on follow-up neuroimaging[18-19]. The incidence of imaging alterations could be ten times greater than some permanent neurological sequelae [16]. Most RIC are asymptomatic and when symptomatic usually are transient. The pathophysiology of RIC remains incompletely understood, although several mechanisms have been posited. The classic radiologic appearance of RIC as perinidal T2 hyperintensity on follow-up MRIs may be a product of blood brain barrier disruption and cerebral edema[20].

There is a hypothesis that all patients will develop some type of RIC, symptomatic or not as part of the natural process of obliteration. Generally, they do not require any specific treatment. When symptomatic, medical therapy with corticosteroids can be administered for weeks to months[21].

Concerning efficacy, a 80% occlusive rate can occur even after 2 years in selected patients. Usually, at least 6 months are necessary to notice neuroimaging changes[22]. Even though uncommon, another SRS session could be proposed to complete the treatment if necessary.

Endovascular treatment

Another type of treatment is the endovascular embolization (Figure 1). This approach is performed using Onyx that is an embolic agent composed of ethylenevinyl alcohol dissolved in DMSO that was approved for neuroendovascular treatments[23]. The efficacy of Onyx for occluding the AVM, however, is not relevant. When the nidus is small, it can be an option, nevertheless usually there are other better options for the definitive treatment. It is necessary to catheterize the feeding arteries of the AVM, with the goal of filling the nidus and occluding feeding vessels while preserving collateral vessels to the normal adjacent brain[1].

Most often, partial embolization has been used to prepare the AVM for definitive microsurgical resection[24]. In some cases, before SRS. Preliminary embolization in arteriovenous malformations causes a staged reduction in blood flow improving the disturbed regional vascular autoregulation[25]. Because embolization occludes deep arterial feeding vessels, surgical morbidity and deficits are reduced since less white matter dissection is required[26].

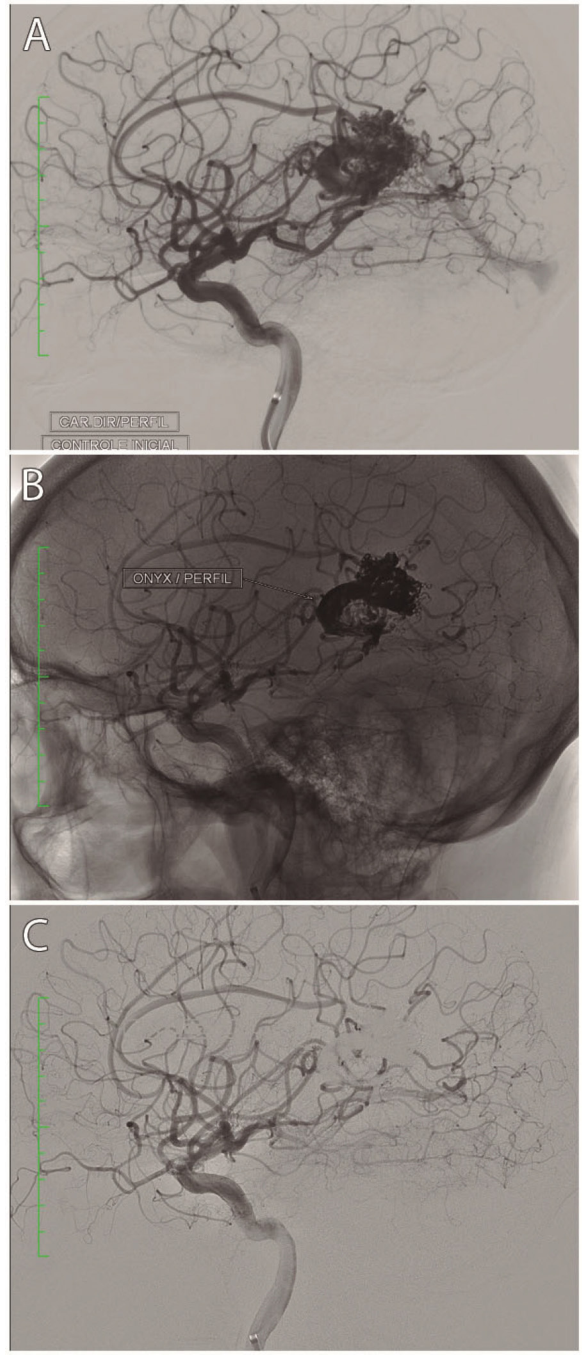

Figure 1 - cerebral angiography (right internal carotid artery injection – lateral view) showing: A – parietal AVM; B – after the endovascular treatment with the onyx injection; C – the absence of early venous opacification, confirming the cure of the AVM.

On the other hand, a notorious endovascular use in this treatment context is for intranidal coil aneurysm embolization and for fistulas occlusions. These associated lesions must be treated before the AVM's surgical removal. Cerebral AVMs multimodality treatments using Onyx embolization followed by SRS is safe, provided that a heterogeneity correction is implemented in order to avoid increased radiation exposure to normal surrounding brain tissue or under-treatment of the nidus. The target volume is smaller after embolization and so less radiation is required. There is a potential obliteration delay time when compared to primarily surgically treated AVMs.

Microsurgery

The third and most important modality is microsurgery that is the gold standard for managing brain AVMs since it is a definite treatment. Despite other less invasive treatments, such as SRS and embolization, surgery remains the main approach for AVMs because of a higher rate of cure.

A craniotomy is necessary for microsurgical assessment and cure. A large exposure of the AVM including its arterial feeders and venous outflow is required [27]. The nidus should be carefully dissected from adjacent white matter to avoid injury, that's why pre-operative embolization is helpful in reducing the AVM's size [7]. The main advantages of microsurgical resection over other treatment options includes its high rate of complete nidus obliteration, its ability to immediately eliminate hemorrhage risk, and its long-term durability. The hemodynamics changes occur quickly on the contrary of SRS that can occur only after two years as such, bleeding can occur during this process.

Many times, patients only discover the diagnosis of an AVM after it ruptures and are seen in an emergency department. Sometimes the hematoma is huge and a surgical approach should be performed in an emergency regime. However, it is more common that these hematomas not require an immediate surgical approach and so the doubt remains: is it worth to operate an AVM in an acute phase or wait? Some studies conclude that there is no benefit in waiting for a delayed approach [6], specially because nowadays other treatment options are available. It is well known that surgery in the acute phase is more difficult because of modified anatomy and so an incomplete occlusion could be performed.

Despite the ARUBA trial defence of a conservative approach for unruptured AVMs, this result was not accepted by many specialists. Other studies consider that even low grade AVMs (by Spetzler-Martin), if ruptured, can evolve with higher morbidity and mortality, as so, surgery, embolization or SRS should be performed before[28].

Conclusion

Treatment of cerebral AVMs requires careful preoperative evaluation ideally performed by a multidisciplinary team. The best selected treatment method, be it isolated or combined, should be performed according to the particular characteristics of each case, always aiming at complete resection or total obliteration of the AVM. Microsurgical resection is still considered the gold standard method for the treatment of these lesions. Currently, the use of endovascular embolization and radiosurgery for the management of AVMs, either alone or in conjunction with microsurgery, is increasing.

References

1. Solomon RA, Connorlly ES Jr. Arteriovenous malformations of the brain. N Engl J Med. 2017; 376(19):1859-66.
2. Furlan AJ, Whisnant JP, Elveback LR. The decreasing incidence of primary intracerebral hemorrhage: a population study. Ann Neurol. 1979; 5(4):367-73.
3. Fennell VS, Martirosyan NL, Atwal GS, Kalani MYS, Ponce FA, Lemole GM Jr, et al. Hemodynamics associated with intracerebral arteriovenous malformations: the effects of treatment modalities. Neurosurgery. 2017; 83(4):611-21.
4. Magro E, Gentric JC, Batista AL, Kotowski M, Chaalala C, Roberge D, et al. The treatment of brain AVMs study (TOBAS): an all-inclusive framework to integrate clinical care and research. J Neurosurg. 2017: 128(6):1823-9.
5. Kaplan HA, Aronson SM, Browder EJ. Vascular malformations of the brain. J Neurosurg. 1961; 18(5):630-5.
6. Hafez A, Oulasvirta E, Koroknay-Pál P, Niemelä M, Hernesniemi J, Laakso A. Timing of surgery for ruptured supratentorial arteriovenous malformations. Acta Neurochir. 2017; 159(11):2103-12.
7. Derdeyn CP, Zipfel GJ, Albuquerque FC, Cooke DL, Feldmann E, Sheehan JP, et al. Management of brain arteriovenous malformations: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2017; 48(8):e200-24.
8. Morgan MK, Davidson AS, Assaad NNA, Stoodley MA. Critical review of brain AVM surgery, surgical results and natural history in 2017. Acta Neurochir. 2017; 159(8): 1457-78.
9. Spetzler RF, Martin NA. proposed grading system for arteriovenous malformations. J Neurosurg. 2008; 108(1): 186-93.
10. Pollock BE, Storlie CB, Link MJ, Stafford SL, Garces YI, Foote RL. Comparative analysis of arteriovenous malformation grading scales in predicting outcomes after stereotactic radiosurgery. J Neurosurg. 2016; 126(3):852-8.
11. Starke RM, Kano H, Ding D, Lee JY, Mathieu D, Whitesell J, et al. Stereotactic radiosurgery for cerebral arteriovenous malformations: evaluation of long-term outcomes in a multicenter cohort. J Neurosurg. 2016; 126(1):36-44.
12. Dandy WE. Venous abnormalities and angiomas of the brain. Arch Surg. 1928; 17(5):715-93.
13. Cushing H, Bailey P. Tumors arising from the blood vessels of the brain: angiomatose malformations and hemangioblastomas. Springfield: Charles C Thomas: 1928. p. 105-9.
14. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): A multicentre, non-blinded, randomised trial. Lancet. 2014; 383(9917):614-21.
15. Mohr JP, Hartmann A, Kim H, Pile-Spellman J, Stapf C. Viewpoints on the ARUBA trial. 2015. AJNR Am J Neuroradiol; 36(4):615-7.
16. Ilyas A, Chen CJ, Ding D, Buell TJ, Raper DMS, Lee CC, et al. Radiation-induced changes after stereotactic radiosurgery for

brain arteriovenous malformations: a systematic review and meta-analysis. Neurosurgery. 2018; 83(3):365-76.
17. Kano H, Flickinger JC, Tonetti D, Hsu A, Yang HC, Flannery TJ, et al. Estimating the risks of adverse radiation effects after gamma knife radiosurgery for arteriovenous malformations. Stroke. 2017; 48(1):84-90.
18. Blamek S, Boba M, Larysz D, Rudnik A, Ficek K, Eksner B, et al. The incidence of imaging abnormalities after stereotactic radiosurgery for cerebral arteriovenous and cavernous malformations. Acta Neurochir Suppl. 2010; 106:187-90.
19. Bose R, Agrawal D, Singh M, Kale SS, Gopishankar N, Bisht RK, et al. Draining vein shielding in intracranial arteriovenous malformations during gamma-knife. Neurosurgery. 2015; 76(5):623-32.
20. Massengale JL, Levy RP, Marcellus M, Moes G, Marks MP, Steinberg GK. Outcomes of surgery for resection of regions of symptomatic radiation injury after stereotactic radiosurgery for arteriovenous malformations. Neurosurgery. 2006; 59(3):553-9.
21. Nagy G, Grainger A, Hodgson TJ, Rowe JG, Coley SC, Kemeny AA, et al. Staged-volume radiosurgery of large arteriovenous malformations improves outcome by reducing the rate of adverse radiation effects. Neurosurgery. 2017; 80(2):180-92.
22. Strauss I, Haim O, Umansky D, Corn BW, Frolov V, Shtraus N, et al. Impact of onyx embolization on radiosurgical management of cerebral arteriovenous malformations: treatment and outcome. World Neurosurg. 2017; 108:656-61.
23. Maimon S, Strauss I, Frolov V, Margalit N, Ram Z. Brain arteriovenous malformation treatment using a combination of onyx and a new detachable tip microcatheter, SONIC: Short-term results. AJNR Am J Neuroradiol. 2010; 31(5):947-54.
24. Eliava S, Dmitriev A, Shekhtman O, Yakovlev S, Kheireddin A, Pilipenko Y. Treatment of brain arteriovenous malformations with hemodynamic aneurysms: a series of 131 consecutive cases. World Neurosurg. 2018; 110:e917-27.
25. Young WL, Kader A, Ornstein E, Baker KZ, Ostapkovich N, Pile-Spellman J, et al. Cerebral hyperemia after arteriovenous malformation resection is related to "breakthrough" complications but not to feeding artery pressure. Neurosurgery. 1996; 38(6):1085-93.
26. Starke RM, Komotar RJ, Otten ML, Hahn DK, Fischer LE, Hwang BY, et al. Adjuvant embolization with N-butyl cyanoacrylate in the treatment of cerebral arteriovenous malformations: outcomes, complications, and predictors of neurologic deficits. Stroke. 2009; 40(8):2783-90.
27. Ogilvy CS, Stieg PE, Awad I, Brown RD Jr, Kondziolka D, Rosenwasser R, et al. 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. 2001; 103(21):2644-57.
28. Cenzato M, Tartara F, D'Aliberti G, Bortolotti C, Cardinale F, Ligarotti G, et al. Unruptured versus ruptured avms: outcome analysis from a multicentric consecutive series of 545 surgically treated cases. World Neurosurg. 2018; 110:e374-e382.

Article received: December 14, 2020
Article approved: March 12, 2021
Article published: April 19, 2021