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Combination Treatment of Cerebral Arteriovenous Malformations Using Endovascular and Microsurgical Techniques

D.M. GALAKTIONOV, A.V. DUBOVOY, V.S. KISELEV, A.O. SOSNOV, K.S. OVSYANNIKOV, A.M. PERFIL'EV, A.V. CHEREPANOV

Federal Center of Neurosurgery, Novosibirsk, Russia

Material and methods. The study included 40 patients with cerebral AVMs. In the study group, 14 (35%) patients underwent microsurgical resection without preliminary embolization (1st group), and 26 (65%) patients underwent combined treatment (endovascular embolization and microsurgical intervention, 2nd group). The first group included patients with S&M grade I—III AVMs, and the second group included patients with S&M grade II—V AVMs. Treatment outcomes were evaluated with allowance for completeness of AVM resection, operative blood loss, duration of surgery, changes in clinical and neurological impairments according to the modified Rankin scale, and rate of neurological and surgical complications.

Results. According to postoperative findings, AVMs were totally resected in all patients. Persistent focal neurological symptoms developed in 2 (7.7%) cases in the second group; neurological complications occurred in 1 (7.1%) patient in the first group. The mean blood loss during resection of AVMs without preliminary embolization and embolized AVMs in patients with S&M grade I—III AVMs was 271.4 mL and 149.1 mL, respectively. The duration of surgery and blood loss did not differ significantly in microsurgery and combination treatment groups.

Conclusion. Combination treatment, including microsurgical intervention after endovascular embolization, is an effective treatment for AVMs, in particular for high grade (S&M grade III—V) AVMs. Teamwork and coordination among the surgeon, endovascular surgeon, and radiologist in treatment of AVMs is a prerequisite for a good outcome.

Keywords: *arteriovenous malformation, combination treatment, surgical treatment of AVM, preoperative embolization.*

According to the literature [1], the detectability of clinically manifested arteriovenous malformations (AVMs) equals about 1 case per 100,000 population per year. Clinical manifestations of AVM occur most frequently as a result of its rupture and intracranial hemorrhage [1]. The risk of AVM hemorrhage is approximately 2—4% per year. Moreover, 18% of hemorrhage cases result in lethality, while 38—53% of the cases lead to neurological deficit [2].

To date, there are 3 methods of treating AVM: microsurgical, endovascular, and radiological techniques. These methods are used alone or in combination with each other. The choice of the treatment approach primarily depends on the capabilities of the hospital, preferences of the medical team and significantly differs between clinical centers [3]. In addition, the opinions of various surgeons on the benefits of endovascular embolization prior to open surgical intervention are contradictory. According to the majority of authors, preoperative embolization allows reducing the size of the vascularized area of AVM, reduces the risk of intraoperative hemorrhage, technically facilitates AVM resection and thereby improves the functional outcome of microsurgical intervention [4—6]. At the same time, a number of authors [7] point out that preoperative embolization increases disability and mortality chances when used in combination treatment.

The study presents analysis of the results of combination treatment of AVM (endovascular embolization and microsurgical resection) conducted at Novosibirsk Federal Center of Neurosurgery.

Material and Methods

The study included 40 patients (20 males, 20 females, aged 18 to 69 years (mean age 40.5±14.2 years)) with cerebral AVM operated on at Novosibirsk Federal Center of Neurosurgery in the period from February, 2013 to October, 2015.

All patients underwent a comprehensive examination including clinical and neurological examination, recording of complaints and medical history, consultations with related specialists: ophthalmologist, otoneurologist, and therapist. Furthermore, all patients underwent instrumental examination: computed tomography (CT) of the brain, multidetector CT angiography (SCT), magnetic resonance imaging (MRI) of the brain, cerebral angiography (CA).

Clinical manifestation of the disease was associated with hemorrhage in 13 (32.5%) patients and with epileptic syndrome in 14 (35%) patients. One (2.5%) patient developed ischemic symptoms of acute impairment of cerebral circulation on the vascular territory adjacent to the AVM. A total of 12 (30%) patients were diagnosed with AVM due to the complaints of headache, dizziness and other manifestations of chronic cerebral circulatory insufficiency.

Headache prevailed among the study patients (16 (40%) cases). Pyramidal insufficiency due to a previous hemorrhage in the region of motor tracts was detected in 3 (7.5%) patients, visual impairments and aphasic disorders were noted in 2 (5%) and 2 (5%) patients, respectively. One (2.5%) patient had ataxia due to a previous

e-mail: d_galaktionov@neuronsk.ru

hemorrhagic stroke in the cerebellar hemisphere; dizziness and visual hallucinations were observed in 2 (5%) and 1 (2.5%) patients, respectively.

The degree of disability was assessed in all patients using the modified Rankin's scale (mRS, 1988) **(Fig. 1)**. The majority (42.5%) of the patients had no functional disorders prior to surgery (0 mRS points). AVM was localized in the right hemisphere in 20 (50%) cases and in the left hemisphere in 18 (45%) cases. AVM was most frequently observed in the temporal lobe (complete or partial localization): 18 (45%) patients in total. Two (5%) patients were diagnosed with cerebellar AVM. The localization of AVM in the studied patients is presented in **Table 1**.

Preoperative evaluation of AVM was carried out using the Spetzler and Martin (S&M) scale [8]. S&M grade II and III AVM patients (17 (42.5%) and 15 (37.5%) patients, respectively) prevailed in the study **(Fig. 2)**.

Microsurgical resection of AVM without preliminary embolization was performed in 14 (35%) patients (group 1), combination treatment (endovascular embolization and microsurgical resection) was performed in 26 (65%) patients (group 2).

Group 1 consisted of patients with S&M grade I—III AVM, group 2 included patients with S&M grade II AVM (**see Fig. 2**).

Endovascular embolization of AVM was performed using transfemoral arterial access under combined endotracheal anesthesia and controlled hypotension. As an embolic agent, cyanoacrylates were used in 6 (23.1%) cases, non-adhesive Onyx polymer was applied in 13 (50%) cases, and combination of adhesive sealant and non-adhesive agents was used in 7 (26.9%) patients.

The degree of AVM embolization was evaluated using CT angiography images in two planes based on the volume of the contrast medium as a percentage of the initial figures. The amount of AVM embolization before surgery had an average value of 84.5%, median value of 90%, interquartile range of 75; 96.5 (minimum volume, 50%; maximum volume, 100%).

All of the patients underwent control CT of the brain immediately after endovascular surgery in order to exclude possible hemorrhage, ischemia and vasogenic edema.

One-stage embolization was performed in 12 (46.2%) cases, 2-stage, 3-stage and 4-stage embolization was conducted in 8 (30.8%), 2 (7.7%) and 1 (3.8%) patients, respectively, prior to AVM resection. Three (11.5%) patients underwent ⩾5 embolizations.

All surgeries were scheduled. The terms between the last embolization and microsurgical intervention varied from a few hours to 10 months depending on the results of control CA and the patient's consent to the next stage of surgical treatment. The period between the last embolization and surgical intervention averaged 45.2 days; median, 7 days; interquartile range, 4; 75.2 days.

In the combined treatment group, 10 (38.5%) patients were changed to open surgical intervention due to the technical impossibility of further embolization, which was established based on the results of control CA performed in the period of 3—6 months from the last embolization. The impossibility of embolization was associated with the lack of available afferents for catheterization and putative high risk of complications during embolization due to the functional significance of afferents. Microsurgical intervention was the original method of choice in 16 (61.5%) patients.

Osteoplastic trepanation of the skull was performed with AVM node resection in all cases at the stage of open surgical treatment. In all patients, intervention was carried out under endotracheal anesthesia combined with controlled hypotension. The position on the operating table was determined by AVM localization and the selected type of access. Head was firmly fixed in the Mayfield clamp. Preoperative planning was carried out using a frameless navigation system. The size of the trepanation window, as a rule, exceeded the size of malformation, the dura mater was opened along the edge of the bone defect. The main stage was performed using a surgical microscope and intraoperative contact Doppler sonography.

The following parameters were taken into account in evaluation of the results of surgical treatment: completeness of AVM resection, operative blood loss, duration of surgery, changes in disability according to the modified Rankin scale, and the rate of neurological and surgical complications.

Statistical processing of the obtained data was carried out using R ver. 3.2.4 software (R Foundation). The methods of descriptive statistics were used for analysis of the study results: calculation of the arithmetic mean (M), standard deviation (m), median (Me), lower and upper quartiles. Normality of distribution was verified using the Shapiro—Wilk test. The Welch's t-test (normally distributed values), the Mann—Whitney's U test, and the exact Fisher's test with modification for contingency tables larger than 2×2 were used for comparison of the groups. The correlation was determined using the Spearman

***Table 1.* Distribution of patients by AVM localization**

Localization	Number of patients, %
Temporal lobe	13 (32.5)
Parietal lobe	6 (15)
Frontal lobe	10 (25)
Occipital lobe	3 (7.5)
Frontal and temporal lobes	2 (5)
Temporal and occipital lobes	1 (2.5)
Parietal and occipital lobes	1 (2.5)
Frontal, parietal and temporal lobes	1 (2.5)
Parietal and temporal lobes	1 (2.5)
Cerebellar hemisphere	2 (5)
Total	40 (100)

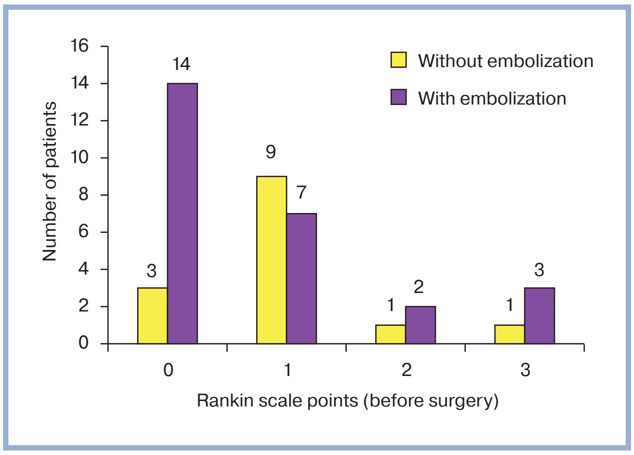

Fig. 1. **Distribution of group 1 and 2 patients according to the Rankin scale prior to surgery.**

method. Differences were considered statistically significant at $p<0.05$.

Results

Groups 1 and 2 were comparable in gender ($p=1.0$), age ($p=0.42$) and the degree of functional disorders and disability according to the Rankin scale ($p=0.11$) but statistically significantly differed in patient distribution according to the S&M scale ($p=0.04$).

Subtraction CA was performed in 8 (20%) patients in the postoperative period, the remaining patients underwent SCT. According to the examination data, AVM was completely resected in all patients.

There were no deaths. One patient with S&M grade II AVM localized in the occipital lobe developed stable quadrant homonymous hemianopsia after endovascular embolization, which persisted after microsurgery. One patient with S&M grade V AVM localized in the right temporal lobe developed left-sided hemiparesis of up to 3 points associated with ischemia in the capsula interna due to the occlusion of perforating arteries after the third stage of embolization.

Thus, persistent focal neurological symptoms developed in 2 (7.7%) cases in group 2.

Neurological complications were noted in 1 (7.1%) cases after microsurgical interventions: a patient with S&M grade II AVM of the left frontal lobe developed mild paresis of the facial nerve and motor aphasia symptoms, which partially regressed during therapy.

Surgical complication in the form of hematoma of 30 mL in the bed of the resected AVM occurred in 1 (7.1%) patient from the first group. This complication was clinically manifested in the form of hemiparesis, which developed on the first day after surgery. The patient underwent revision of the operative wound and hematoma resection. No signs of residual AVM were observed during revision. Neurological symptoms regressed completely after repeated surgery. In 2 (7.7%) patients of the second group, ligature fistulas were formed after 1.5—2 months, which required revision of the postoperative scar and fistula excision.

Analysis of neurological disorders and the degree of disability after surgery according to the modified Rankin scale showed that 1 (7.1%) patient of the first group experienced negative changes (1-point deterioration). Among the second group patients, 1 (3.8%) patient showed deterioration by 1 point and another (3.8%) patient experienced 3-point deterioration **(Fig. 3)**. There were no statistically significant differences.

Comparison of the volume of blood loss and surgery duration between the groups was conducted only among patients with S&M grades I—III AVM (14 patients of the group 1, 22 patients of the group 2), which was caused by the absence of S&M grades IV—V patients in the group 1. Mean blood loss in the group 1 was 271.4 mL (median, 100 mL; interquartile range, 50 to 250 mL). Mean blood loss in the group 2 was 149.1 mL (median, 100 mL; interquartile range, 50 to 200 mL). There were no statistically significant differences in blood loss between the groups (Mann—Whitney test, $p=0.664$).

Mean duration of surgery was 290.4±104.3 min in group 1 and 280.7±97.1 min in group 2. There were no

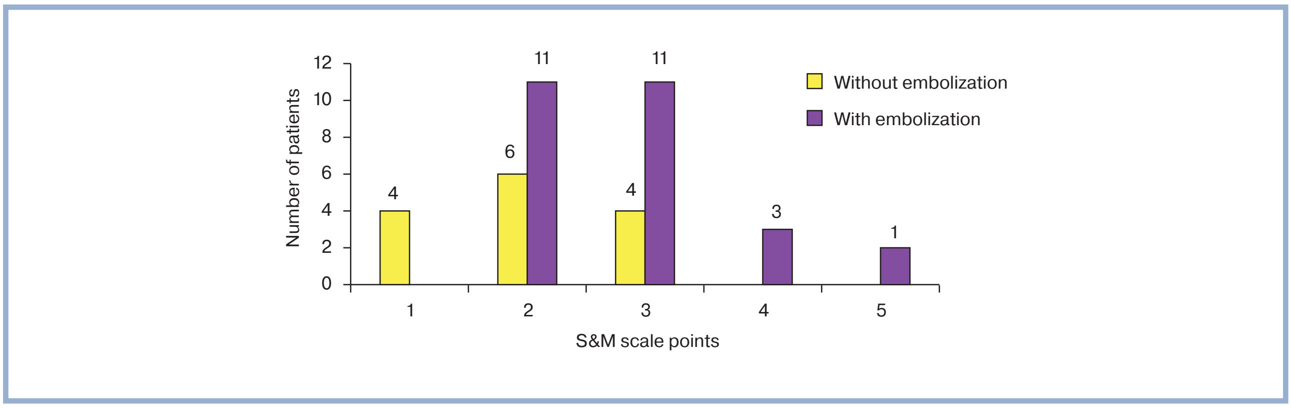

Fig. 2. **AVM distribution in groups 1 and 2 according to the S&M scale.**

statistically significant differences in surgery duration between the groups (Student's test p=0.78).

Mean blood loss was 50, 50, 700 and 1000 mL, respectively, in 4 patients of the group 2 with S&M grade IV—V AVM, the duration of surgery was 205, 330, 600 and 365 min, respectively.

No correlation was revealed during analysis of the effect of amount of embolization on blood loss in group 2 patients.

Discussion

Microsurgical resection, which provides early improvement and subsequently reduces the risk of hemorrhage to practically zero, is the most radical method of AVM treatment [9]. It can be solely performed only in patients with a low risk of surgery. The risk is associated with hard-to-reach sources of AVM blood supply, intranidal aneurysms, large fistulas, large linear dimensions and volume of AVM, localization in functionally important areas.

Total occlusion of AVM can be achieved by endovascular intervention in 16—32.8% of cases [10—12]. Some authors [13] present higher rates of AVM embolization: 51%, with a 2—8.7% risk of complications and a mortality rate of 0.8—3%. According to A. Nataraj et al. [2], residual AVMs are found after treatment in patients with high-grade AVM after embolization as the only method of treatment in 41% of cases, while microsurgical resection results in only 2% of residual AVMs. Moreover, incomplete occlusion does not prevent re-hemorrhage, and, according to some data [2, 14, 15], increases the risk of hemorrhage compared to patients who have not received any treatment at all. According to our observations, as well as according to some authors, even after complete AVM obliteration according to angiographic criteria, the residual filling of the AVM center through the feeding vessels is determined during the subsequent microsurgical surgery [6].

Taking into account low completeness, intravascular interventions for AVM are currently being considered primarily as a preliminary stage for more radical methods: microsurgical resection or radiation. Endovascular embolization allows reducing the AVM volume and the amount of arteriovenous shunting, shutting off the feeding arteries that are difficult to access in direct intervention and areas of malformation that are potentially dangerous with respect to rupture.

In our study, 26 patients were treated using combination approach (endovascular + microsurgical methods). There were no deaths; the incidence of persistent neurological disorders was 7.7%.

According to the article by R. Crowley et al. [16], which demonstrates the results of treatment of 342 patients with AVM, the relationship between the number of the stages of endovascular intervention and neurological complications was revealed (the average number of embolization stages with complications was 1.57±0.75, the average number of embolization stages without complications was 1.26±0.53, p=0.01). Postoperative neurological complications and deaths accounted for 11.4%. L. Kim et al. [17] revealed a direct relationship between the S&M grade of AVM and the rate of complications. In 2009, R. Starke et al. [18] published results of the treatment of 202 patients who underwent embolization prior to microsurgical resection or radiosurgery: postoperative neurological deficit developed in 14% of cases. It has been established that the risk factors for postoperative neurological disorders are the need for more than one embolization, AVM diameter is less than 3 cm or more than 6 cm, deep venous drainage, and localization in the functionally significant region.

According to the literature data [6], the complication rates of combined treatment vary widely and reach 28.6%, severe complications of combined treatment and lethality are found in 4.6—7% and 2.3% of cases, respectively.

In our study, the mean blood loss during combined treatment of the patients with S&M grade II—III AVMs was 149.1 mL (median 100 mL), the duration of surgery was 280.7 min. These results are comparable to the blood loss values for the group with microsurgical intervention. Similar results were obtained in the study by O.D. Shekhtman et al. [12] presenting a comparative analysis conducted between the two groups (40 patients with AVM underwent preliminary embolization and 40 patients were subjected to microsurgical resection of AVM only). There were no significant difference in the mean duration of surgery and blood loss, which exceeded the standard value (more than 500 mL), between the study and control groups. In the work by S. Natarajan et al. [6], the mean blood loss in the group of 28 patients with an average S&M grade of 2.75, who underwent combined treatment, with an average embolization rate of 74.1%, was 348 mL. In our study, we managed to minimize the blood

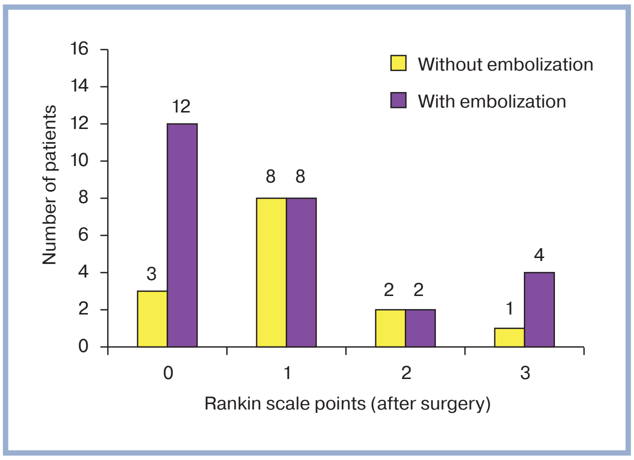

Fig. 3. **Distribution of group 1 and 2 patients according to the Rankin scale after surgery.**

loss and decrease the duration of surgery in a series of cases with S&M grade IV—V AVM. These results are comparable with the results obtained for the group of patients with S&M grade I—III AVM, which is due to the positive effect of preliminary embolization on the technical aspects of microsurgical intervention. Moreover, subjectively speaking, preliminary embolization technically simplifies the microsurgical resection of the AVM center, allows performing dissection as close as possible to the site and avoiding damage to the surrounding brain tissue. Embolization allows one to switch off the deeply located afferents that limit the excision of the S&M grade IV—V AVM [2].

We have not revealed any correlation between the blood loss and the degree of embolization. In addition, we have not found any indications of a "golden mean" between the degree of AVM embolization and the rate of ruptures and neurological complications that require open surgical intervention in the literature. According to F. Vinuela et al. [5], no effect of embolization was observed in resection of AVM embolized by less than 50%. Embolization of more than 75% of the AVM volume facilitated the dissection, while providing the control over bleeding from the feeding arteries during the intervention.

The decision on the choice of treatment method, number of stages, and the amount of surgical intervention should be made by a multidisciplinary team with participation of a neurosurgeon, an endovascular surgeon, and a radiologist. Microsurgical intervention is preferred in small, S&M grade I—II AVMs that are located superficially and beyond functionally important areas. Taking into account high variability of the grade III AVM, the decision is to be made individually in each particular case; the combined treatment is preferred. Combined treatment is also recommended in grade IV—V AVM.

When choosing a combined treatment strategy (endovascular embolization + microsurgery), it is necessary to strive to reduce the number of endovascular interventions and, maybe, not achieve complete occlusion of AVM (the recommended amount of embolization before microsurgery is more than 75%) [5]. Particular attention should be paid to switching off the deep feeding arteries from the bloodstream. In addition, it is necessary to decrease the time between the last embolization and the microsurgical stage as much as possible to minimize the risk of hemorrhage and AVM recanalization [11].

Conclusion

The treatment of cerebral arteriovenous malformations remains to be one of the most complex and contradictory issues in vascular neurosurgery. As the literature data and the results of our study show, a multidisciplinary approach involving neurosurgeons and endovascular surgeons is required in order to reduce the risk of neurological and surgical complications as well as to increase the completeness of surgical intervention and improve the quality of the patients' life at the modern stage of medical development. Preoperative embolization in patients with high S&M grade AVM allows technical facilitation of AVM resection and reduction in the risks of surgical intervention.

Authors declare no conflict of interest.

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Commentary

The article by D.M. Galaktionov et al. is devoted to an important problem: evaluation of the role of preoperative embolization in increasing the effectiveness of the treatment of cerebral arteriovenous malformations (AVMs).

Cerebral AVM is one of the most complicated cerebrovascular medical condition, which often requires a multidisciplinary approach in the treatment. There are few papers devoted to the issues of combined treatment of AVM. Therefore, the studies in this area are of particular interest.

The study presents analysis of the results of treating patients with cerebral AVM using microsurgical and combined approaches (microsurgical resection after endovascular embolization). I think that the groups to be compared have not been formed quite correctly. A group of patients who initially had to undergo preoperative embolization with subsequent AVM resection was combined with a group who failed to achieve complete endovascular AVM thrombosing (including multistage embolization). Therefore, microsurgical excision of the AVM was performed. In addition, it was often performed in a long period after embolization. This combined group is compared with the group that underwent only microsurgical interventions of AVM removal. Thus, the principle of selecting patients for combined interventions has been violated. Furthermore, when determining the complexity of surgical interventions, one should take into account not only the angioarchitectonics of malformation (the number of afferent arteries and drainage veins, their location and accessibility) but AVM localization as well. For example, AVM of the right frontal lobe with complicated angioarchitectonics is technically easier to resect than the less complex malformations of the mediobasal regions of the temporal lobe. Determination of indications for preliminary endovasal shutdown of the deep afferents of the AVM and the associated malformation sector prior to its microsurgical removal much depends on localization.

Nevertheless, such publications are important, since they reflect the current understanding of the need to coordinate the possibilities of endovasal technique with direct microsurgical interventions to alleviate technical problems that arise during AVM resection, increase the percentage of radical interventions and reduce the number of intraoperative complications.

Sh.Sh. Eliava (Moscow, Russia)