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**Dmytro V. Shcheglov**<sup>1</sup>, Doctor of Medical Science, Neurosurgeon, Director, <https://orcid.org/0000-0003-1465-8738>

**Oleh Ye. Svyrydiuk**<sup>1</sup>, Ph.D., Neurosurgeon, <https://orcid.org/0000-0001-7455-0396>

**Mykola B. Vyval**<sup>1</sup>, Neurosurgeon, <https://orcid.org/0000-0002-9428-4678>

**Svitlana V. Chebanyuk**<sup>1</sup>, Cardiologist, Head of Scientific Department, <https://orcid.org/0000-0002-5644-1951>

**Igor V. Altman**<sup>1</sup>, Vascular Surgeon, <https://orcid.org/0000-0001-7279-4071>

**Maryna Yu. Mamonova**<sup>2</sup>, Ph.D., Assistant of the Department of Anesthesiology and Intensive Care, <https://orcid.org/0000-0002-0697-4864>

<sup>1</sup>Research and Practical Center for Endovascular Neuroradiology of the National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine

<sup>2</sup>Bogomolets National Medical University, Kyiv, Ukraine

## Results of the Treatment and Evaluation of Quality of Life in Patients with High-Grade Cerebral Arteriovenous Malformations after Endovascular Embolization

### Abstract

**Introduction.** Treatment options for cerebral arteriovenous malformations (cAVMs) may include radiosurgery, endovascular embolization, microsurgical removal, or a combination thereof. However, treatment of high-grade (Spetzler–Martin grades IV and V) cAVMs remains extremely challenging when aiming complete occlusion.

**The aim.** To study the safety of the endovascular embolization in patients with high-grade cAVMs and its impact on the quality of life (QoL).

**Materials and methods.** Between 2012 and 2022, 174 patients with cAVMs were endovascularly treated at Research and Practical Center for Endovascular Neuroradiology of the National Academy of Medical Sciences of Ukraine with an average follow-up of more than 9 months. Of these patients, 11 (6.3%) and 6 (3.4%) had Spetzler–Martin grade IV and grade V cAVM, respectively. Outcomes after surgical procedures were assessed and QoL was evaluated using standardized EQ-5D-3L questionnaire.

**Results.** Five (29.4%) patients had intracerebral hemorrhage, 6 (35.3%) had seizures, 5 (29.4%) had other non-hemorrhagic manifestations and 1 (5.9%) patient had a neurological deficit as a result of cerebral steal. In 17 patients, 28 embolization sessions were performed, and in nearly all of them (96%) N-butyl cyanoacrylate was used as the preferred embolic agent. There were no procedural complications. After embolization, three (17.6%) patients had neurologic deterioration (temporary in 2 patients and persistent in 1 patient).

All the patients were alive at the nearest follow-up. After embolization, 2 (11.7%) patients had recurrent hemorrhage, but without additional morbidity. Two of the five patients after cAVM rupture had some degree of disability. With regard to non-hemorrhagic debut, 8 (72%) patients reported symptom reduction. QoL assessment with EQ-5D-3L questionnaire revealed that severe problems were present in 2 (33.3%) of 6 patients after intracerebral hemorrhage and 2 (18.2%) of 11 patients with non-hemorrhagic manifestation. The mean Visual Analogue Scale score for the hemorrhagic group was  $76.4 \pm 15$  points, while the non-hemorrhagic group's score was  $85.2 \pm 14$  points.

**Conclusions.** Endovascular embolization, which aims to occlude the bleeding site or improve cerebral steal with a manageable consequence profile, can be used safely in carefully selected patients with high-grade cAVMs. Our experience shows that QoL can be satisfactory in 3/4 of patients after high-grade cAVM embolization, and more data from real-world practice are highly needed to determine the best method and time for improving patient outcomes.

**Keywords:** *brain malformation, endovascular treatment, intracranial hemorrhage, outcome, modified Rankin Scale, EQ-5D-3L questionnaire.*

**Introduction.** Cerebral arteriovenous malformations (cAVMs) are known as pathological complex network of abnormal connections between dilated cerebral arteries and veins inside the brain parenchyma [1]. Most cAVMs manifest between 10 and 40 years with intracerebral hemorrhage, seizures, focal neurological deficits or headache. The patient's age, the size, the location, and the vascular characteristics of the cAVM all affect how this pathology will manifests clinically. Intracerebral hemorrhage (ICH) is the most typical presenting symptom and is found in 50% of cases, and cAVMs are the main cause of ICH in young adults [2]. The annual rupture risk was reported to be 2.3-3% overall, and 4.5-4.8% for cases that were ruptured [3]. Few cAVM classifications were introduced to improve bleeding risks, anatomical peculiarities and treatment approach, among them Luessenhop–Gennarelli anatomical grading, Spetzler–Martin scale, Nataf scale and Vienna classification [4]. Spetzler–Martin (SM) scale was introduced in 1986 and divides cAVMs by size, location and deep venous drainage and remains the most commonly used [5]. The SM grading scale assigns a score of 1 for small cAVMs (3 cm). The eloquence of adjacent brain is scored as either non-eloquent (0) or eloquent (1). The venous drainage is scored as superficial only (0) or including drainage to the deep cerebral veins (1). It determines two distinct groups: low-grade (grades I, II, and III) and high-grade (grades IV and V) cAVMs. Low-grade cAVMs are usually tiny, superficial, and/or ineloquent. High-grade cAVMs, on the other hand, frequently include expressive brain regions and are big, deep lesions [6].

Microsurgical removal, endovascular embolization, radiosurgery, or combinations of these methods are available treatment options for cAVMs. In case of rupture cAVM treatment is obvious and is aimed at preventing re-ruptures [7]. However, management of unruptured cAVMs is still debated and only one randomized trial (ARUBA) evaluated the results of interventional treatment in such patients, however, it revealed worse clinical outcome compared to observation [8]. Due to plenty of study limitations many authors disagree with these findings. Further observational studies have examined the effectiveness of surgery on ARUBA-eligible patients and revealed favorable safety profiles and cure rates in patients who were carefully selected with different techniques. The authors hypothesize that large prospective randomized trials on cAVMs may not be practical, and practice-based data outside the ARUBA study is warrant to improve patient outcomes over the long term [9]. Expert consensus on the management of cAVMs after ARUBA trial postulate that complete occlusion of cAVM is the only acceptable target of any treatment [7]; however, giant and deep cAVM is often challenging for complete occlusion and brings high risks of morbidity. Otherwise in case of rupture its source should be secured with no doubt, and in case of observation

of non-hemorrhagic manifestation of cAVM symptoms can exacerbate, become debilitated and require treatment to improve patients' quality of life (QoL). Endovascular embolization often remains the only treatment modality for high-grade cAVMs, but according to the current data, it carries the risk of procedural rupture in 7% on each embolization session. In such circumstances, evaluation of the safety of this strategy and its impact on QoL of these patients is needed.

**The aim.** To study the safety of endovascular embolization in patients with high-grade cAVMs and its impact on their QoL.

**Materials and methods.** One hundred and seventy four patients with cAVMs were embolized at the Research and Practical Center for Endovascular Neuroradiology of National Academy of Medical Sciences of Ukraine between 2012 and 2022 with more than 9 months follow-up after the treatment. Of these, 128 (73.6%) patients underwent one endovascular embolization procedure, 46 (26.4%) patients underwent multi-session endovascular embolization. The mean age of the patients was  $38 \pm 2.1$  years; there were 102 (58.6%) men and 41 (41.4%) women. Hemorrhagic manifestation was reported in 106 (60.9%) patients. Sixty-one (35.1%) patients had seizures and 7 (4.0%) patients had other type of non-hemorrhagic debut (1 case of local neurological deficit, 4 cases of intractable headache, and in 2 cases cAVM was an accidental finding during neuroimaging after traumatic brain injury). All the patients were classified according to

**Table 1**

*Study population according to Spatzler-Martin scale before embolization*

cAVM characteristics		Number of patients (%)
Localization	Cerebral lobes (frontal, parietal, temporal, occipital)	114 (65.5)
	Corpus callosum	4 (2.3)
	Basal ganglion	25 (14.4)
	Thalamus	6 (3.4)
	Cerebellum	18 (10.3)
SM grade	Grade I	70 (40.2)
	Grade II	55 (31.6)
	Grade III	30 (17.2)
	Grade IV	11 (6.3)
	Grade V	6 (3.4)
Size	< 3 cm	59 (33.9)
	3-6 cm	95 (54.6)
	> 6 cm	20 (11.5)
Drainage	Deep	47 (27.0)
	Superficial	92 (52.9)
	Combined	35 (20.1)

SM scale, and 17 (9.8%) patients with high-grade cAVMs were revealed (data are summarized in Table 1). There were 11 (6.3%) patients with SM grade IV and 6 (3.4%) patients with SM grade V.

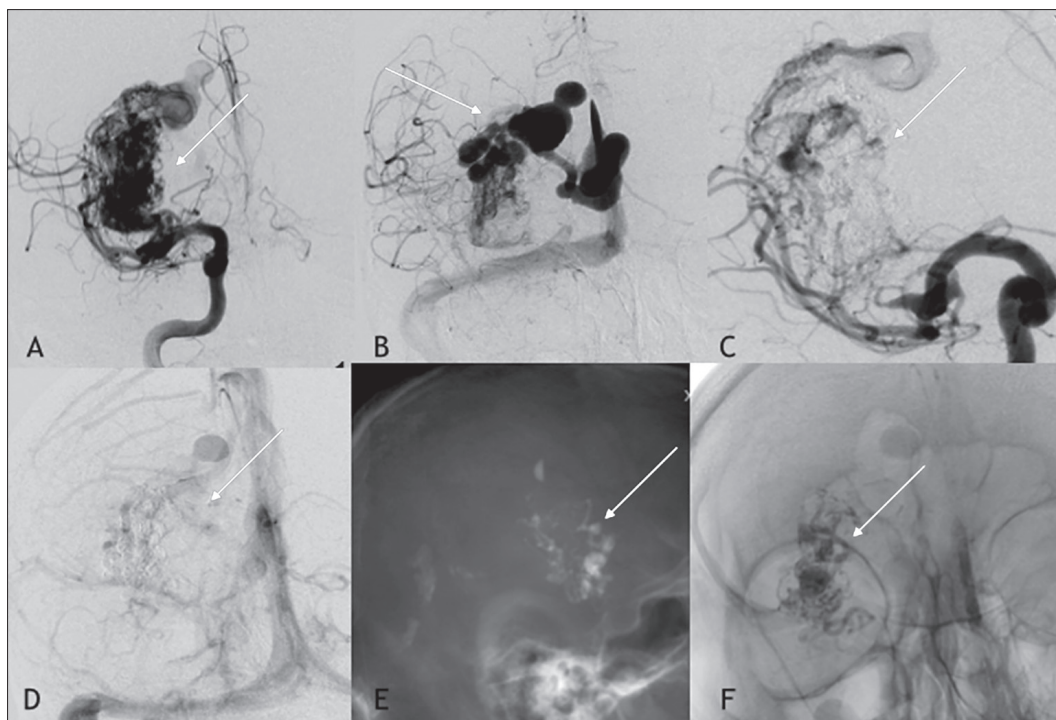
All the patients underwent complete physical examination and standard laboratory tests. Data collection during hospitalization included a detailed analysis of the patients' history, manifestations, and course. All the patients received standard medical care and treatment after the procedure. The embolization strategy consists in eradication of hemodynamic disturbances and correction of the cerebral steal, elimination of the direct arteriovenous (AV) shunts, exclusion of associated aneurysms as the source of rupture. The patients were informed about the risks of the procedure and signed consent form. For endovascular embolization, liquid embolic agents (LEAs) (mixture of N-butyl cyanoacrylate (nBCA, Histoacryl, B. Braun, AG Melsungen, Germany) with ethiodized oil (Lipiodol, Guerbet LLC) and ethylene vinyl alcohol copolymer (Onyx, EV3, Irvine, CA, USA)) with additional detached coils (if necessary) were used. The procedure was performed under general anesthesia with mild hypotension through femoral access under heparinization (10 000 U). 6F femoral sheath was inserted and guiding catheter was placed in internal carotid artery or vertebral artery, then microcatheter (Magic or Sonic [Balt,

Montmorency, France], depending on LEA) was navigated to the selected vessel and embolization was performed. Results of surgical interventions were evaluated based on postoperative angiograms. All the surgical reports were analyzed to evaluate procedural complications and surgical technique. Results of the treatment were assessed according to modified Rankin Scale (mRS).

**QoL assessment.** We measured QoL using the standardized EQ-5D-3L questionnaire [10] which consists of a three-level scale in five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). The Visual Analogue Scale measures the patient's actual general health on a scale of 0 to 100, with 0 being the worst possible state of health and 100 representing the best possible state. The patients were divided into two groups according to manifestation (hemorrhagic and non-hemorrhagic). They were interviewed during different time of follow-up (9-96 months, mean 28.8 months).

Due to the limited sample size we employed descriptive statistics only, and data were presented as mean  $\pm$  SD.

**Results and discussion.** Among 17 patients, 5 (29.4%) had ICH, 6 (35.3%) had seizures, 5 (29.4%) had other non-hemorrhagic manifestations (headache, vertigo, tinnitus, etc.) and 1 (5.9%) patient experienced neurological deficit because of cerebral steal (right arm paresis, and



**Fig. 1.** A 46-year-old female patient with intracerebral hemorrhage due to high-grade cAVM rupture with multiple intranidal aneurysms (A and B). She underwent partial embolization with N-butyl cyanoacrylate (C, D, E and F) and was successfully discharged with no neurological deficits. After 4.5 years she had moderate symptoms with no disability

**Table 2***Radiological peculiarities in patients with high-grade cAVMs*

Characteristics	Values
Age, years	28.6
Sex, males/females	9/8
Associated aneurysms, number of patients with high-grade cAVM (%)	6 (35.3)
High-flow shunts, number of patients with high-grade cAVM (%)	10 (58.8)
Number of embolization sessions	
1	9 (52.9)
2	5 (29.4)
3	3 (17.6)
Embolization materials	
NBCA	27 (96.4)
ONYX	1 (3.6)
mRS on admission for hemorrhagic group, mean $\pm$ SD	2.2 $\pm$ 1.2
mRS on discharge for hemorrhagic group, mean $\pm$ SD	1.8 $\pm$ 0.7
mRS on admission for non-hemorrhagic group, mean $\pm$ SD	0.6 $\pm$ 0.3
mRS on discharge for non-hemorrhagic group, mean $\pm$ SD	0.5 $\pm$ 0.4

cAVM was misdiagnosed since early childhood in favor of cerebral palsy). There were 28 embolization session in 17 patients, and almost all of them were made with N-butyl cyanoacrylate (NBCA) (96.4%) as preferable LEA

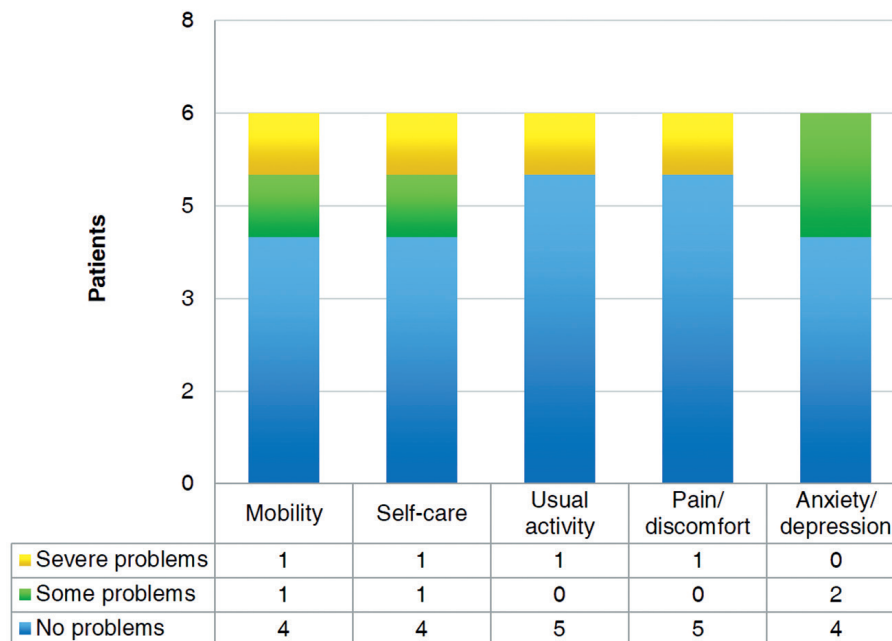
(Fig. 1 and Table 2). Additional utilization of detached coils was done during two procedures in order to reduce flow in the AV shunts and avoid excessive spreading of LEA.

There were no procedural complications, and all embolization sessions were successful considering the nidus reduction and elimination of high-flow AV shunts and associated aneurysms. Three patients (17.6%) had neurologic deterioration after embolization, and two of them were transient. One patient (5.8%) had persistent hemianopsia that was present on follow-up. Postoperative period was unremarkable in other patients and improvement of mRS score at discharge was noted.

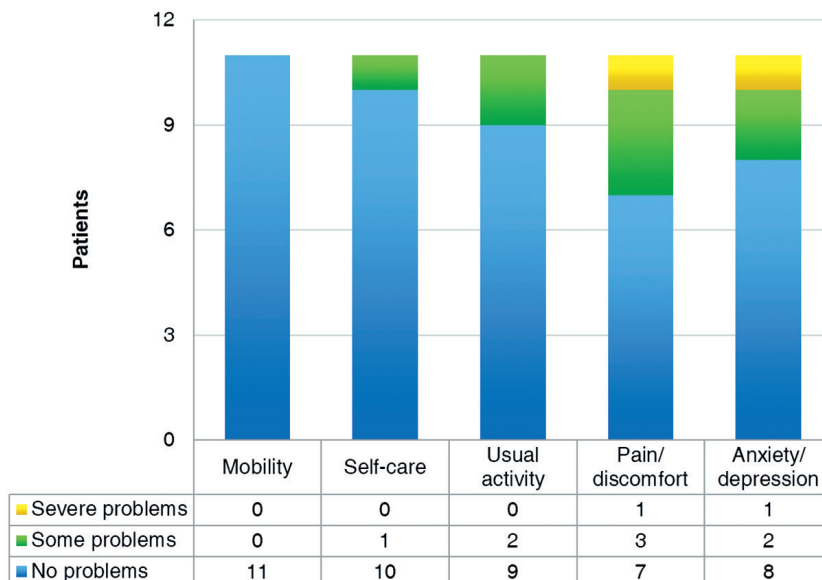
Two patients with hemorrhagic debut were transferred to rehabilitation department due to neurological deficits (mRS 3). Mean hospital stay was 16.4 days for hemorrhagic debut and 6.4 days for non-hemorrhagic.

By the nearest follow-up all the patients were alive. Two patients (11.7%) had hemorrhage after embolization, first one after 1.5 years (hemorrhagic debut) and another one (with seizures) 4 years after the procedure. However, hemorrhages were small, parenchymal and non-fatal. Both patients recovered after hemorrhage and didn't experience additional morbidity. Among 5 patients with cAVM rupture, 2 experienced some degree of disability (mRS 2 and 3, respectively), and 3 were completely independent. Among those with non-hemorrhagic debut, 8 (72.7%) patients showed symptom reduction and 3 (27.3%) patients remained the same or got worse.

QoL assessment with EQ-5D-3L questionnaire revealed that severe problems were present in 2 (33.3%) of



**Fig. 2.** Number of patients with cAVMs with hemorrhagic manifestations by level within EQ-5D-3L dimensions



**Fig. 3.** Number of patients with cAVMs with non-hemorrhagic manifestations by level within EQ-5D-3L dimensions

6 patients after ICH (Fig. 2) as a result of neurologic deficits and 2 (18.2%) of 11 patients with non-hemorrhagic manifestations; interestingly, these problems were not connected to daily activity, self-care or mobility, but in one case they were accompanied by anxiety/depression and in another one by pain (Fig. 3).

The mean Visual Analogue Scale score was  $76.4 \pm 15$  points in hemorrhagic group and  $85.2 \pm 14$  points in non-hemorrhagic one.

High-grade cAVMs (SM grades IV and V) are challenging to treat with any existing modalities. And if these lesions are asymptomatic, observation is mandatory, but in case of manifestations, like rupture or debilitated non-hemorrhagic debut, treatment becomes optional, and the unique ability to target specific parts of cAVM makes endovascular embolization one possible solution for this lesions. Although targeted embolization is not curative in high-grade cAVMs, it may be useful in reducing bleeding site, like intranidal aneurysm [11], venous ectasias and stenosis [12] or improve cerebral steal [13]. However, it required experienced evaluation and judicious approach of this strategy as it can increase complication rates and increase morbidity [14, 15, 16]. Also the choice of LEA is essential for successful procedure. Our preferred LEA for high-grade cAVM was NBCA, and we didn't experience procedural problems, considering partial and target embolization as well as prevention of unaffected occlusion of draining vein. Considering ARUBA data, worldwide trend of conservative approach for unruptured cAVMs brings some controversial results. Dicipinigaitis et al. reported the incidence of ruptured cAVM increased in the post-ARUBA trial era (13.3% versus 34.4%;  $P < 0.001$ ) as

well as rates of in-hospital mortality (2.0% versus 7.6%;  $P < 0.001$ ) [17]. Our small series revealed rupture after embolization in 11.7% of patients with mean follow-up of nearly 5 years, that is less than 37% reported by A. Laakso et al., but with longer follow-up [18]. Also we didn't found additional procedural complications after embolization.

Considering that the aim of interventional treatment of cAVMs is complete occlusion, and in case of high-grade cAVM, this approach can be risky. And in case of incomplete occlusion risk of hemorrhage and evaluation of the QoL seems reasonable for evaluation of treatment success. Our data shows that up to 75% of patients with high-grade cAVM had no serious problems with their QoL after endovascular embolization, and the risk of hemorrhage is at least compatible to that in natural course. Nevertheless, current data shows that evidence is still lacking to make some ideal recommendations for cAVM, and hopefully this will change in the nearest future.

Our study has few limitations, it is retrospective without control group. Also, some patients were lost to follow-up, so their results could influence the final conclusions. However, main aim of our study was to show the effective utility of endovascular embolization in carefully selected patients with high-grade cAVMs. Further studies are needed to strengthen the evidence base and improve patient selection for any of the treatment modality.

### Conclusions

1. High-grade (SM grades IV and V) cAVMs are a challenging pathology and require multidisciplinary approach.
2. Endovascular embolization was safely utilized in carefully selected patients with high-grade cAVMs,

aiming to occlude bleeding site or improve cerebral steal with acceptable complication profile. Three patients (17.6%) had neurologic deterioration after embolization, and two of them were transient. One patient (5.8%) had persistent hemianopsia that was present on follow-up.

2. Recurrent hemorrhage after partial cAVM embolization was seen in 11.7% of patients; however, these were small, parenchymal and non-fatal.
3. Our experience demonstrates that QoL after high-grade cAVMs embolization can be satisfactory in 3/4 of the patients, but further studies are needed to evaluate the best treatment strategy for these patients.

**Conflict of interest.** All authors declare that they have no conflicts of interest.

**Patient consent.** Obtained.

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## Результати лікування та оцінювання якості життя пацієнтів із церебральними артеріовенозними мальформаціями високого ступеня після ендovasкулярної емболізації

Щеглов Д. В.<sup>1</sup>, д-р мед. наук, лікар-нейрохірург, директор

Свиридюк О. Є.<sup>1</sup>, канд. мед. наук, лікар-нейрохірург

Виваль М. Б.<sup>1</sup>, лікар-нейрохірург

Чебанюк С. В.<sup>1</sup>, канд. мед. наук, заступник директора з наукової роботи, лікар-кардіолог

Альтман І. В.<sup>1</sup>, канд. мед. наук, лікар судинний хірург

Мамонова М. Ю.<sup>2</sup>, канд. мед. наук, асистент кафедри анестезіології та інтенсивної терапії

<sup>1</sup>ДУ «Науково-практичний центр ендovasкулярної нейрорентгенохірургії НАМН України», м. Київ, Україна

<sup>2</sup>Національний медичний університет імені О. О. Богомольця, м. Київ, Україна

### Резюме

**Вступ.** Варіанти лікування артеріовенозних мальформацій (АВМ) головного мозку включають ендovasкулярну емболізацію, радіохірургію, мікрохірургічне видалення або їх комбінацію. Однак лікування АВМ високого ступеня (ступені IV і V за Spetzler–Martin) залишається надзвичайно складним.

**Мета** – вивчити безпеку ендovasкулярної емболізації пацієнтів з АВМ головного мозку високого ступеня та її вплив на якість життя пацієнтів.

**Матеріали та методи.** З 2012 по 2022 рік у ДУ «Науково-практичний центр ендovasкулярної нейрорентгенохірургії НАМН України» ендovasкулярно проліковано 174 пацієнти з АВМ із середнім терміном спостереження понад 9 місяців. Серед них 11 (6,3 %) пацієнтів мали АВМ IV-го ступеня за Spetzler–Martin та 6 (3,4 %) пацієнтів – АВМ V-го ступеня за Spetzler–Martin. Результати після хірургічних втручань оцінювали за допомогою стандартизованого опитувальника EQ-5D-3L.

**Результати.** У 5 (29,4 %) пацієнтів мав місце внутрішньомозковий крововилив, у 6 (35,3 %) – судоми, у 5 (29,4 %) – інші негеморагічні прояви, в 1 (5,9 %) пацієнта – неврологічний дефіцит внаслідок «синдрому обкрадання». У 17 пацієнтів було проведено 28 сеансів емболізації, і майже всі з них (96 %) з використанням n-Butyl суаноасулате як емболічної речовини. Не було виявлено перипроцедурних ускладнень. Після емболізації у 3 (17,6 %) хворих спостерігалось неврологічне погіршення, з них у 2 тимчасове, в 1 (5,8 %) – стійке.

Усі пацієнти були живі під час найближчого огляду. Після емболізації у 2 (11,7 %) хворих виникли повторні кровотечі, але без додаткової інвалідизації. Двоє з п'яти пацієнтів після розриву АВМ мали певний ступінь інвалідності. Що стосується негеморагічного дебюту, 8 (72 %) пацієнтів повідомили про зменшення симптомів. Оцінювання якості життя за допомогою опитувальника EQ-5D-3L показала, що серйозні проблеми відзначалися у 2 (33,3 %) з 6 пацієнтів після розриву АВМ та у 2 (18,2 %) з 11 пацієнтів з негеморагічними проявами. Середній бал за шкалою VAS для групи з геморагією становив  $76,4 \pm 15$  бала, а для групи без геморагії –  $85,2 \pm 14$  бала.

### Висновки

1. АВМ головного мозку високого ступеня (ступені IV і V за Spetzler–Martin) є складною патологією і потребують мультидисциплінарного підходу.

2. Ендovasкулярна емболізація була успішно проведеною у ретельно відібраних пацієнтів з АВМ високого ступеня з метою оклюзії місця кровотечі або покращення церебрального обкрадання з прийнятним профілем ускладнень. У 3 пацієнтів (17,6 %) після емболізації спостерігалось неврологічне погіршення, у 2 з них – транзиторне. В 1 пацієнта (5,8 %) дефіцит залишився стійким.

3. Повторні крововиливи після часткової емболізації АВМ спостерігалися в 11,7 % пацієнтів. Однак вони були невеликими, паренхіматозними та нелетальними.

4. Наш досвід показує, що якість життя після високоякісної емболізації АВМ може бути задовільною у 3/4 пацієнтів, але необхідні подальші дослідження, щоб оцінити найкращий метод лікування та його терміни для покращення результату для пацієнтів.

**Ключові слова:** вада розвитку головного мозку, ендovasкулярне лікування, внутрішньочерепний крововилив, результат, модифікована шкала Ренкіна, опитувальник EQ-5D-3L.

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