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Research Article

Safety and Efficacy of Intraoperative Indocyanine Green and Sodium Fluorescein Use in AVM Surgery

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Abstract

Aim: In our study, authors retrospectively analyzed the outcomes of 14 patients who underwent surgery using microsurgical techniques with the aid of intraoperative Na-Fl and ICG angiography. Our aim was to highlight the importance and advantages of using Na-Fl and ICG during AVM surgery.

Material and Methods: Authors retrospectively evaluate the outcomes of 14 AVM patients who underwent surgery with the aid of Na-Fl (Akorn, Inc.) at American Hospital (Istanbul, Türkiye) and Liv Hospital (Istanbul, Türkiye) and to demonstrate the benefits provided by the use of Na-Fl (Akorn, Inc.) and ICG (Verdye, Diagnostic Green GmbH, Aschheim, Germany) during surgery. All patients underwent preoperative cerebral angiography, and their AVMs were graded according to the Spetzler-Martin classification except one patient with spinal AVM. Angioarchitecture of AVMs were identified using the Yellow 560 filter of the Kinevo 900 surgical microscope (Carl Zeiss Meditec, Oberkochen, Germany) and ICG angiography with INFRARED 800 filter. In all patients, early postoperative control digital subtraction angiography (DSA) was performed.

Results: Eight (57.15%) of the patients were male and six (42.85%) were female. The mean age of the patients was 57.26 ± 21.38 years. According to the Spetzler-Martin classification, 5 patients had Grade I AVMs, 3 had Grade II, and 5 had Grade III AVMs. One patient had a glomus type cervical intramedullary AVM. Hemorrhagic AVMs were present in six (42.85%) patients, while eight (57.15%) patients had non-hemorrhagic AVMs. None of the patients required reoperation for residual AVM. Importantly, no adverse reactions or complications related to Na-Fl or ICG administration were observed in any patient, demonstrating the safety profile of these fluorescent agents at the administered doses.

Conclusion: Given their complementary advantages and limitations, the combined use of these videoangiography techniques in AVM surgery offers a more comprehensive, reliable, and effective intraoperative assessment.

Keywords: Sodium fluorescein angiography, Indocyanine green angiography, microsurgery

INTRODUCTION

Arteriovenous malformations (AVMs) are the most common type of intracranial vascular malformations and the leading cause of non-traumatic intracerebral hemorrhage in youth under 35 years of age (1). In a study conducted in Western Australia, the incidence of AVM's was reported as 0.89/100,000 and also a similar study conducted in Scotland it was found to be 1.12/100.000 with a prevalence of 15-18/100.000 (2, 3). AVMs can present with seizures, headaches, focal neurological deficits, and bleeding. In the literature, it has been reported that bleeding occurs in approximately 50% of AVM presentations (4). Meta-analysis studies conducted to determine bleeding risk of AVM, showed that previous hemorrhage history, location of the AVM and presence of deep venous drainage can be associated with the risk of future bleeding (5). In their meta-analysis study, Gross and Du found that the annual bleeding risk for all AVM's was 3%. They reported a bleeding risk of 2.2% for unruptured AVMs and 4.5% for rup-

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tured AVM's (5). Studies on the natural course of AVMs in the literature have found the annual bleeding risk to be between 2% and 5% (6). This risk is reported to increase fivefold in cases of ruptured AVMs (7). AVM hemorrhages lead to a fatal outcome in 5-25% of patients (8).

Current treatment options for AVM's include observation, surgical resection, embolization, stereotactic radiosurgery, and combined treatment strategies. Comparing the estimated lifetime risk with the risk of the preferred treatment method plays an important role in deciding the type of AVM's (9). Although there are different treatment approaches for AVM, surgical intervention stands out as the most effective approach for Grade 1 and 2 AVMs according to the Spetzler-Martin classification (6, 10). In AVM surgery, it is crucial to disconnect the feeding arteries, avoid damaging en passage vessels, and preserve the draining vein until the end of the procedure. As AVMs have complex vascular anatomy, the use of real-time intraoperative angiographic methods such as sodium fluorescein (Na-Fl) and indocyanine green (ICG) angiography are safe and effective techniques that facilitate the identification of feeding and en passage vessels as well as the draining vein (11, 12).

In our study, we retrospectively analyzed the outcomes of 14 patients who underwent surgery using microsurgical techniques with the aid of intraoperative Na-Fl and ICG angiography. Our aim was to highlight the importance and advantages of using sodium fluorescein and ICG during AVM surgery.

MATERIAL AND METHODS

In our study, we aimed to retrospectively evaluate the outcomes of 14 AVM patients who underwent surgery with the aid of Na-Fl (Akorn, Inc.) at American Hospital (Istanbul, Türkiye) and Liv Hospital (Istanbul, Türkiye), and to demonstrate the benefits provided by the use of sodium fluorescein and ICG (Verdye, Diagnostic Green GmbH, Aschheim, Germany) during surgery. Ethical approval for this retrospective study was obtained from the Ordu University Ethics Committee (decision number: 2025/260). Written informed consents were obtained from all patients. All patients underwent preoperative cerebral angiography, and their AVMs were graded according to the Spetzler-Martin classification except one patient with spinal AVM (13). During surgery, the feeders and venous drainage of the AVMs were identified using the Yellow 560 filter of the Kinevo 900 surgical microscope (Carl Zeiss Meditec, Oberkochen, Germany) and ICG angiography with INFRARED 800 nm filter. In all patients, early postoperative control digital subtraction angiography (DSA) was performed. All patients underwent surgery under general anesthesia. After exposing the AVM through a craniotomy of appropriate size, 1 ml (100 mg) of Na-Fl was intravenously injected in all patients for video angiography. Approximately 20 seconds later, using the Yellow 560 filter of the surgical microscope, the arterial, venous, and capillary phases of the cerebral angiography became visible. Na-Fl angiography enabled real-time manipulation of the vessels. Following Na-Fl video angiography, 25 mg of ICG was intravenously administered to all patients, and ICG video angiography was performed. If necessary, an additional 1 ml (100 mg) of 10% Na-Fl and 25 mg of ICG were administered for repeated videoangiography assessments. The recommended dose for angiography is 0.2 to 0.5 mg/kg with a maximum dose of 5 mg/kg/day. Vessel fluorescence was visible within seconds and was cleared within 10 minutes, allowing for additional injections. The total dosage did not exceed 5 ml (500 mg) of Na-Fl and 5 mg/kg of ICG. After identifying the feeders and venous drainage of the AVM, the feeders were coagulated, the draining vein was occluded, and the surgery was completed with hemostasis. No adverse reactions related to Na-Fl or ICG administration were observed in any patient during or after the procedures, confirming the safety of these agents within the recommended dosage ranges.

Statistical Analysis

Statistical analysis was performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and median with range, while categorical variables were presented as frequencies and percentages. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. For continuous variables, independent samples t-test was used for normally distributed data, while the Mann-Whitney U test was applied for non-normally distributed data. Categorical variables were analyzed using Chi-square test or Fisher's exact test, as appropriate. The relationship between Spetzler-Martin grade and hemorrhagic presentation was evaluated using Spearman's correlation coefficient. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Eight (57.1%) of the patients were male and six (42.9%) were female. The mean age of the patients was 57.26 ± 21.38 years. According to the Spetzler-Martin classification, 5 (38.5%) patients had Grade I AVMs, 3 (23.1%) had Grade II, and 5 (38.5%) had Grade III AVMs. One patient had a glomus type cervical intramedullary AVM. Hemorrhagic AVMs were present in six (42.9%) patients, while eight (57.1%) patients had non-hemorrhagic AVMs (Table 1). Analysis of the relationship between Spetzler-Martin grade and hemorrhagic presentation revealed a statistically significant positive correlation (Spearman's rho = 0.685, p = 0.010). Specifically, hemorrhage was present in 1 of 5 patients (20.0%) with Grade 1 AVMs, 1 of 3 patients (33.3%) with Grade 2 AVMs, and 4 of 5 patients (80.0%) with Grade 3 AVMs. High-grade AVMs (Grade 3) demonstrated a statistically significant higher hemorrhage rate compared to low-grade AVMs (Grades 1-2) (80.0% vs. 25.0%, p = 0.048, Fisher's exact test). (Table 2) This 3.2-fold increase in hemorrhagic presentation among Grade 3 AVMs compared to lower grades represents a clinically and statistically significant finding, suggesting that higher Spetzler-Martin grades are strongly associated with increased risk of hemorrhagic presentation.

Table 1. Demographic and Clinical Characteristics of Patients with AVMs

Characteristic	Value
Patient Demographics	
Total number of patients	14
Gender, n (%)	
Female	6 (42.9)
Male	8 (57.1)
Age, years	
Mean ± SD	57.26 ± 21.38
Median (range)	37.0 (19-78)
Follow-up Duration	
Mean ± SD, months	67.4 ± 24.8
Median (range), months	72.5 (32-96)
Anatomical Localization, n (%)	
Temporal	6 (42.9)
Frontal	4 (28.6)
Posterior fossa	2 (14.3)
Temporoparietal	1 (7.1)
Cervical spinal	1 (7.1)
Spetzler-Martin Grade*, n (%)	
Grade 1	5 (38.5)
Grade 2	3 (23.1)
Grade 3	5 (38.5)
Clinical Presentation, n (%)	
Hemorrhagic	6 (42.9)
Non-hemorrhagic	8 (57.1)
Associated Aneurysm, n (%)	2 (14.3)
Main Arterial Feeders, n (%)	
MCA	7 (50.0)
ACA	5 (35.7)
ATA	3 (21.4)
AICA/PICA/SCA	2 (14.3)
Spinal arteries (ASA/PSA)	1 (7.1)
Primary Venous Drainage, n (%)	
Superior sagittal sinus	6 (42.9)
Transverse sinus	3 (21.4)
Sigmoid sinus	2 (14.3)
Sylvian veins	2 (14.3)
Vein of Galen	1 (7.1)

**Spetzler-Martin grading applied to intracranial AVMs only (n=13)*
SD: Standard deviation, MCA: Middle Cerebral Artery, ASA: Anterior Spinal Artery, PSA: Posterior Spinal Artery, ATA: Anterior Temporal Artery, AICA: Anterior Inferior Cerebellar Artery, PICA: Posterior Inferior Cerebellar Artery, ACA: Anterior Cerebral Artery, SCA: Superior Cerebellar Artery, AVM: Arteriovenous Malformation

The mean follow-up duration was 67.4 ± 24.8 months (range: 32-96 months), with a median follow-up of 72.5 months. All patients completed at least 32 months of follow-up, with the longest follow-up extending to 96 months. The most common localization was the temporal lobe, accounting for 6 cases (42.9%), followed by frontal lobe in 4 cases (28.6%). Posterior fossa AVMs were present in 2 patients (14.3%). One patient each had temporoparietal (7.1%) and cervical spinal (7.1%) AVMs. Among intracranial AVMs, supratentorial locations predominated (11/13, 84.6%). (Table 1)

Analysis of arterial feeders demonstrated that the middle cerebral artery (MCA) was the most common feeding vessel, supplying 7 AVMs (50.0%). The anterior cerebral artery (ACA) supplied 5 AVMs (35.7%), either alone or in combination with MCA. The anterior temporal artery (ATA) served as a feeder in 3 cases (21.4%). Posterior fossa AVMs were supplied by cerebellar arteries (AICA, PICA, and/or SCA) in 2 patients (14.3%). The single spinal AVM received supply from anterior and posterior spinal arteries. (Table 1)

Venous drainage patterns showed that the superior sagittal sinus (SSS) was the most common drainage pathway, present in 6 cases (42.9%). Other drainage routes included transverse sinus in 3 cases (21.4%), sigmoid sinus in 2 cases (14.3%), Sylvian veins in 2 cases (14.3%), and the vein of Galen in 1 case (7.1%). (Table 1)

In the postoperative period, one patient developed House-Brackmann Grade III 7th cranial nerve paresis, which improved to Grade I by the 6-month follow-up after physical therapy and rehabilitation. In another patient with cervical intramedullary AVM, preoperative quadriparesis showed marked improvement by the 1-year follow-up following physical therapy. Postoperative angiography confirmed complete excision of the AVM in all patients. None of the patients required reoperation for residual AVM. Two patients had previously undergone surgery at an external center due to intracerebral hematoma, and AVM excision was performed in our clinic. In two patients with AVMs located in the temporal and frontal regions, associated internal carotid artery (ICA) and middle cerebral artery (MCA) aneurysms were detected. These aneurysms were found to be related to flow alterations caused by the AVM. In the control angiography performed after AVM excision, no filling of the aneurysms was observed. In the case with an AVM located in the frontal region and an associated ICA aneurysm, control DSA showed no filling of the aneurysm following complete resection of the AVM. In the case with an AVM in the temporal region and an MCA aneurysm, persistent filling of the aneurysm was observed after total excision of the AVM, and the aneurysm was subsequently clipped.

Illustrative cases

case 1

A 20-year-old male patient was diagnosed with an non-hemorrhagic AVM, classified as Spetzler-Martin Grade II, during the evaluation of dizziness. Neurological examination revealed no focal deficits. Surgical resection was performed via a right frontal craniotomy with the assistance of Na-Fl and ICG videoangiography for intraoperative vascular visualization. The AVM was noted to receive arterial supply from branches of the middle cerebral artery and anterior cerebral artery, with venous drainage into the superior sagittal sinus. Postoperative cerebral DSA confirmed complete resection with no evidence of residual AVM (Figure 1). The postoperative course was uneventful, with no observed complications.

Table 2: Relationship Between Spetzler-Martin Grade and Hemorrhagic Presentation

Spetzler -Martin Grade	Total Patients (n)	Hemorrhagic n (%)	Non- hemorrhagic n (%)	Hemorrhage Rate (%)
Grade 1	5	1 (20.0)	4 (80.0)	20.0
Grade 2	3	1 (33.3)	2 (66.7)	33.3
Grade 3	5	4 (80.0)	1 (20.0)	80.0*
Low-grade (1-2)	8	2 (25.0)	6 (75.0)	25.0
High-grade (3)	5	4 (80.0)	1 (20.0)	80.0*

**p = 0.048 (Fisher's exact test, comparing Grade 3 vs. Grades 1-2)*
Spearman's correlation coefficient: rho = 0.685, p = 0.010

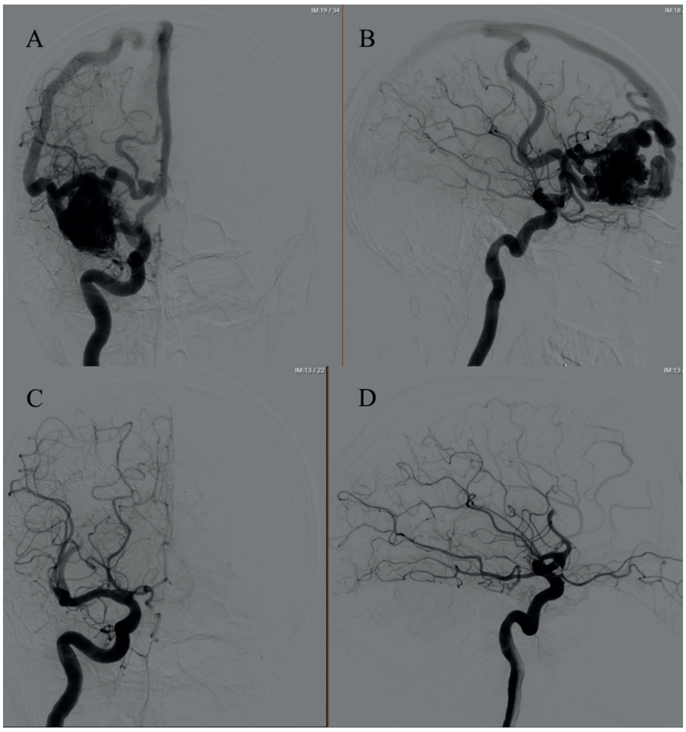

Figure 1. A and B-) Coronal and sagittal view of the DSA showing the main feeders (MCA, ACA) and venous drainage (SSS) of the right frontal AVM. C and D-) Coronal and sagittal view of the postoperative DSA showing the total removal of AVM without any residual flow. MCA: Middle Cerebral Artery ACA: Anterior Cerebral Artery SSS: Superior Sagittal Sinus

case 2

A 20-year-old female patient without any comorbidities was brought to the emergency department of an external center with a complaint of sudden-onset altered consciousness. Imaging revealed an intracerebral hematoma extending from the right cerebellum to the brachium pontis. The right cerebellar intracerebral hematoma was evacuated via craniotomy. Cerebral angiography revealed an AVM predominantly supplied by the right superior cerebellar artery and, to a lesser extent, by the right anterior inferior cerebellar artery, draining into the right basal vein. The patient underwent AVM excision using the existing right suboccipital craniotomy at our center. No residual AVM was observed on postoperative angiography (Figure 2).

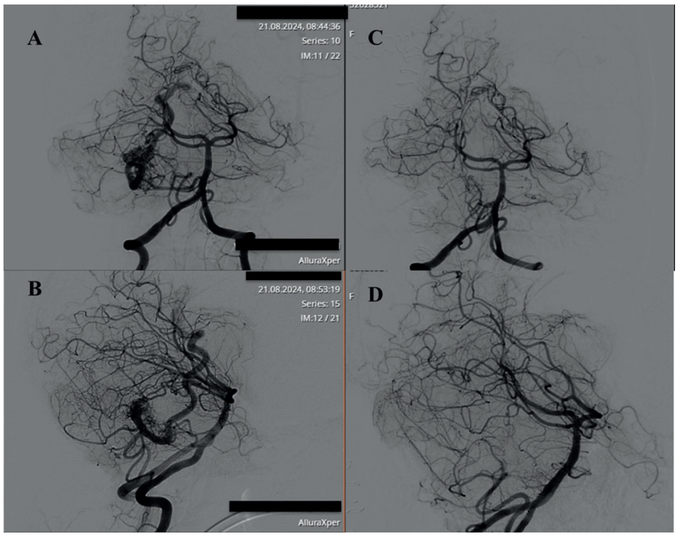

Figure 2. A and B-) Coronal and sagittal view of the DSA showing the main feeders (SCA, AICA) and venous drainage (BV) of the right Cerebellar AVM. C and D-) Coronal and sagittal view of the postoperative DSA showing the total removal of AVM without any residual flow. SCA: Superior Cerebrallar Artery AICA: Anterior Inferior Cerebellar Artery BV: Basal vein

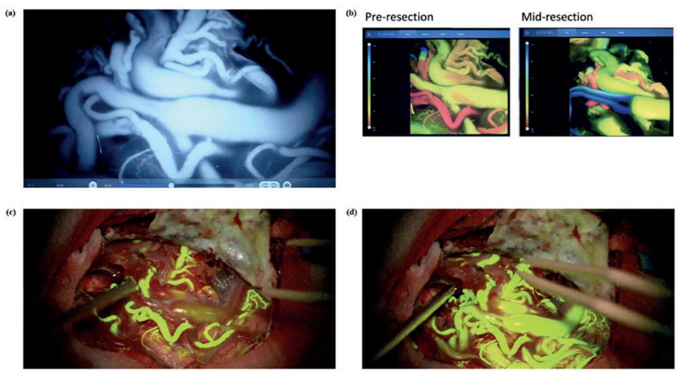

Figure 3. a) A right temporal AVM in a 33-year-old man was demonstrated with ICG-Videoangiography b) Flow-800 module showing pre- and midresection dynamics of the AVM c) Na-Fl Videoangiography showing early arterial phase of the AVM. d) Na-Fl videoangiography showing after venous phase of the AVM.

DISCUSSION

The use of Na-Fl and ICG videoangiography in AVM surgery offers significant advantages as intraoperative imaging tools. Both modalities provide real-time visualization of vascular architecture and blood flow, aiding in the precise identification of arterial feeders, the AVM nidus, and draining veins. These techniques enhance the surgeon's ability to achieve complete resection while minimizing damage to surrounding normal brain tissue.

Intraoperative cranial DSA has long been regarded as the gold standard in vascular neurosurgery for confirming complete resection of AVMs and aneurysm obliteration, as well as for assessing cerebral blood flow (14-16). While still highly valuable in hybrid operating rooms, its routine use in standard surgical settings presents challenges. The global adoption of hybrid operating rooms remains limited due to several constraints, such as the high cost of equipment and the relatively extended duration of the intervention (14, 16). Due to the need for a hybrid operating room and the challenges associated with intraoperative DSA, ICG and Na-Fl videoangiography have become the preferred methods today (12).

Although ICG videoangiography is frequently used in vascular surgery today, it is only visible under near-infrared light due to its wavelength, making it invisible under normal light. Therefore, it does not allow real-time manipulation of vessels during ICG videoangiography. As a result, intraoperative assessment cannot be performed in real time; ICG angiography can only be reviewed retrospectively through the microscope monitor or oculars after the angiography is completed (17). On the other hand, Na-Fl angiography can be monitored in real time during surgery using the Yellow 560 filter of the microscope, allowing for the manipulation of vessels during the procedure and providing a significant advantage. In our study, both videoangiography techniques were reasonably effective in intraoperatively visualizing the feeding arteries and draining veins. However, Na-Fl videoangiography allowed for real-time manipulation of the vessels, which enabled the surgeon to better understand the angioarchitecture of the AVM and facilitated the disconnection of the feeding arteries and draining veins.

In the study conducted by Taddei and colleagues involving 9 patients diagnosed with AVM, ICG angiography was reported to be effective in detecting residual disease (18). Similarly, Hanggi and colleagues shared their experience with 13 patients and demonstrated that ICG angiography was useful in identifying residual AVMs and visualizing the main passage vessels (19). In a case report presented by Takagi and colleagues, no residual disease was detected on peroperative DSA in a patient with a diffuse-type AVM; however, residual AVM was identified in cerebral DSA nine-days after the operation. During repeat surgery, residual nidus was disclosed by using ICG angiography and removed (20). In our study, no patients required reoperation due to residual AVM. However, in one patient with a temporal AVM accompanied by an MCA aneurysm, intraoperative ICG angiography following total excision of the AVM revealed filling of the aneurysm, which was subsequently clipped. Postoperative DSA showed no filling of the aneurysm. There are publications in the literature suggesting that ICG videoangiography may be inadequate compared to intraoperative cranial DSA in visualizing deeply located vascular lesions. ICG videoangiography provides information about the vasculature within the microscopic surgical field during AVM surgery. Therefore, intraoperative DSA is considered superior to videoangiography techniques in detecting feeders, draining veins, and/or residual AVMs situated deep within the brain tissue and outside the microscope's field of view. While ICG and Na-Fl angiography techniques offer insights into the vascular structures visible within the surgical field under the microscope, they may be insufficient for identifying deeply located feeders, draining veins, and for visualizing vascular lesions with complex anatomy when compared to intraoperative DSA (21).

ICG videoangiography provides a real-time, high resolution view of blood flow through cerebral vessels, allowing surgeons to assess vessel patency, clip placement, and residual malformations intraoperatively. Although ICG alone offers valuable information, the addition of the FLOW 800 software module significantly enhances the interpretative power of the technique. FLOW 800 generates color-coded perfusion maps and time-intensity curves based on the dynamics of ICG fluorescence.

These maps illustrate the sequence and speed of blood flow through arteries, capillaries, and veins, enabling identification of hemodynamic changes that may be subtle or difficult to interpret visually (Figure 3). In AVM resection, FLOW 800 supports the identification of arterial feeders and venous drainage pathways. FLOW 800 data effectively illustrates the transition in venous flow patterns during AVM resection, clearly showing a shift from red coloration in the early stages to blue toward the conclusion of the procedure. After resection, the surgeon can use it to confirm the absence of residual nidus. Studies have shown a high concordance between intraoperative ICG-FLOW 800 findings and postoperative DSA supporting its reliability (22-24).

Na-Fl videoangiography enables real-time manipulation of vessel however it has not the advantage of replays for detailed assessment, on contrary to ICG. However, Na-Fl provides more detailed information about the neurovascular anatomy compared to ICG.

Our study demonstrated a statistically significant correlation between higher Spetzler-Martin grades and increased hemorrhagic presentation risk, with Grade 3 AVMs showing an 80% hemorrhage rate compared to 25% in lower grades ($p=0.048$). This finding is consistent with previous literature reporting higher hemorrhage risks in complex AVMs. Stefani et al. demonstrated in a large prospective cohort that deep-seated and larger AVMs were significantly more prone to hemorrhage during follow-up, with deep location showing an odds ratio of 5.56 for future bleeding.(25)

CONCLUSION

High-grade AVMs (Grade 3) demonstrated a statistically significant higher hemorrhage rate compared to low-grade AVMs. The use of sodium fluorescein Na-Fl and ICG videoangiography in AVM surgery offers significant advantages as intraoperative imaging tools. Both modalities provide real-time visualization of vascular architecture and blood flow, aiding in the precise identification of arterial feeders, the AVM nidus, and draining veins. Na-Fl is superior to ICG in deeper surgical fields and enables surgeon for real-time manipulation and ICG provides better understanding of flow dynamics by using FLOW 800 module in AVM surgery. Given their complementary advantages and limitations, the combined use of these videoangiography techniques in AVM surgery offers a more comprehensive, reliable, and effective intraoperative assessment.

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Conflict of Interest

The authors have no conflicts of interest to declare.

Ethical approval

Ethical approval for this retrospective study was obtained from the Ordu University Ethics Committee (decision number: 2025/260).

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