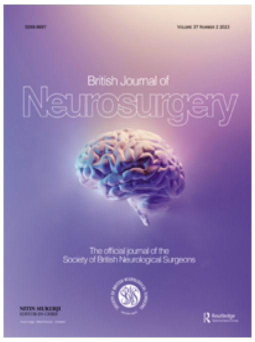

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RESEARCH ARTICLE

Complementary role of Indocyanine green video angiography, dual-image video angiography and flow-800

Khabibullo A. Khasanov[a,b], Gulnara A. Alikhodjayeva[b], Yasuhiro Yamada[a], Yoko Kato[a], Jakhongir B. Yakubov[a,b], Kaan Yağmurlu[c] and Bipin Chaurasia[d]

[a]Fujita Health University Banbuntane Hotokukai Hospital, Nagoya, Japan; [b]Department of Traumatology, Orthopedics, Military-field surgery, and Neurosurgery of Tashkent Medical Academy, Republican Specialized Scientific-Practical Medical Center of Neurosurgery, Tashkent, Uzbekistan; [c]Departments of Neurosurgery and Neuroscience, University of Virginia, USA; [d]Department of Neurosurgery, Neurosurgery Clinic, Birgunj, Nepal

ABSTRACT

Background: Visualization of cerebral vessels, their branches and the surrounding structures are essential during cerebrovascular surgery. Indocyanine green dye-based video angiography is a commonly used technique in cerebrovascular surgery. This paper aims to analyze the real-time imaging of ICG-AG, DIVA, and the use of ICG-VA with Flow 800 to compare their usefulness in surgery.
Methods: Intraoperative real-time identification of vascular and surrounding structures in twenty nine anterior circulation aneurysms and three posterior circulation aneurysm clipping, one STA-MCA bypass, and two carotid endarterectomies were performed in patients using ICG-VA alone, DIVA, ICG-VA with Flow 800 to analyze and compare each of these methods in details.
Results: ICG-VA and DIVA couldn't visualize perforators in twenty-three cases of cerebral aneurysms clipping when used alone. Compared to that by adding Flow 800 perforators were easily visualized. In three cases, occlusion of perforators after clip application was visualized by DIVA and solved by repositioning surgical clips. In one STA-MCA bypass surgery, adequate blood flow to cortical branches of MCA (M4) from STA branches was assessed with ICG-VA, DIVA, and the use of ICG-VA with Flow 800 color mapping. ICG-VA, DIVA, and Flow 800 observed the lack of blood flow and fluttering atherosclerotic plaques in carotid endarterectomy. In one case of basilar tip aneurysm, we used ICG-VA with Flow 800; the intensity diagram drawn after determining regions of interest showed that there was no flow within the aneurysm sac after clipping.
Conclusion: In real-time surgery, a multimodal approach using ICG-VA, DIVA, and ICG-VA with Flow 800 colour mapping can serve as useful tools for better visualization of vascular and surrounding structures. The benefits of flow 800 color mapping, such as determining regions of interest, intensity diagrams, and color-coded images, outweigh the advantages over the ICG-VA and DIVA in the visualization of critical vascular anatomy in humans during surgical procedures.

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KEYWORDS
Indocyanine green video angiography; dual-image video angiography and flow-800; cerebrovascular surgery; aneurysm surgery

1. Introduction

During cerebrovascular surgery, it is crucial to be aware of vascular flow visualization in the surgical field. Surgical microscopes equipped with the near-infrared color camera and optical filter make any challenging cerebrovascular intervention possible and useful. In Real-time surgery Indocyanine green video angiography (ICG-VA) is used to observe vascular circulation in superficial and deep spaces of the human brains for better analysis of the microsurgical anatomy of arteriovenous malformations (AVM), dural arteriovenous fistula (dAVF), intracranial aneurysms, and superficial temporal artery to the middle cerebral artery (STA-MCA) bypass.[1–4] At present, ICG-VA and dual-image video angiography (DIVA) is mostly being used in vascular surgery. During ICG-VA angiography, the near-infrared system detects anatomical and ICG fluorescence signals during operation without image fusion or time delay. Dual image video angiography (DIVA) provides powerful visualization of the vascular circulation concurrently via ICG-angiography under surgical microscopes equipped with innovative laser light which boosts the effectiveness of dual video angiography. This offers visualization of near-infrared (NIR) fluorescence images, clip position and observation of surrounding structures while it is impossible to employ solely ICG video angiography's near-infrared images.[5]

Moreover, in complex aneurysms requiring more than one clip application the small perforators are not visible with ICG-AG. "Flow 800" (Carl Zeiss, Oberkochen, Germany) produces intensity diagrams and color mapping is a new tool to visualize vascular structures better using different colors. These are helpful to distinguish both arterial and venous circulation as well as surrounding structures. The black and white images of conventional ICG-VA cannot differentiate arteries from veins, whereas the red and blue colours of Flow 800 represent arteries and veins respectively. The earlier-arriving ICG explains this differentiation in the fields that belong to the arteries, and those disappearing, at last, belong to the veins.[6] The above-mentioned intraoperative indocyanine-based angiographic visualization techniques of vascular structures do not replace a cerebral angiogram, which has been known as a gold standard for vascular assessment since it can visualize only the vascular system directly within the field of

CONTACT Bipin Chaurasia trozexa@gmail.com Department of Neurosurgery, Neurosurgery Clinic, Birgunj, Nepal

view of a microscope and lacks quantitative interpretation.[6] However, these techniques remain a useful tool in real-time surgery to simultaneously visualize vascular structures. This study analyses and compares the usefulness of the ICG-VA, DIVA, and the use of ICG-VA with Flow 800 color mapping in cerebrovascular surgery.

2. Methods

In Fujita Health University Banbuntane Hotokukai Hospital in Nagoya, Aichi prefecture, Japan, 29 cerebral aneurysms of the anterior circulation, three posterior circulation aneurysms, one STA-MCA bypass and two carotid artery endarterectomy cases underwent surgical treatment from August to October 2019. The study was performed on human subjects under the Declaration of Helinski. ICG-VA and DIVA were used in all cases, and the flow 800 color mapping was performed before and after the surgical procedure like clipping, bypass and endarterectomy in some selected cases. All patients were evaluated and compared by computed tomography (CT), magnetic resonance imaging (MRI), digital subtraction angiography (DSA) and three-dimensional computed tomography angiography (3D-CTA) in pre- and postoperative periods.

The near-infrared color camera MNIRC-200K (Mizuho, Japan. 48mm × 48 mm × 119mm; 0.3kg) integrated into the surgical microscope OPMI PENTERO Flow 800 (Carl Zeiss Meditec, Germany) is also equipped with a particular sensor unit and optical filter to see visible light and NIR fluorescence emission light at 400–700 nm and 800–900 nm respectively and simultaneously. More recently introduced hybrid microscope ZEISS KINEVO 900 (Both by Carl Zeiss Meditec, Jena, Germany) was used to visualize the surgical field fluorescent area and to perform the surgical procedures in addition to the color map of Flow 800 images, hybrid microscope KINEVO 900 in selected cases. As reported by authors,[6] on the color map, red represents the initial blood inflow and the other colors gradients show the subsequent sequences of flow with the identification of feeding arteries, en passage vessels, draining veins, as well as normal cortical arteries and veins. During ICG-AG and DIVA (dual-image video angiography) visualization, ICG 0.3 mg/kg body weight was systemically injected and monitored.

3. Results

Of all 29 anterior circulation aneurysm cases, 12 were male and 17 were female (male to female ratio − 1:1.4). The most common aneurysms are located in the internal carotid artery (ICA aneurysm) of anterior circulation −15 (51.7% of cases), followed by anterior communicating artery (Acom)-6 (20.7%), posterior communicating artery (Pcom)-4 (13.8%), middle cerebral artery (MCA)-3 (10.3%), and anterior cerebral artery (ACA)-1 (3.4%). Aneurysms in anterior circulation predominated posterior circulation with 29(90,6%) and 3(9.4%) (one basilar tip aneurysm and two posterior inferior cerebellar artery aneurysms), respectively. In addition to the cerebral aneurysm clipping and carotid artery endarterectomy, in one STA-MCA bypass procedure, the ICG-VA, DIVA, and ICG-VA Flow 800color mapping were performed. In one case of basilar tip aneurysm, we used Flow 800; the intensity diagram drawn after determining regions of interest showed that there was no flow within the aneurysm sac after clipping. There were no adverse effects of ICG dye in any case. The obtained high-resolution images (ranging from 1280 × 720 pixels to 1980 × 1080 pixels) enabled the surgeon to assess the blood flow in the surgical field. Four cases of three different vascular procedures such as aneurysm clipping, STA-MCA bypass, carotid endarterectomy and, basilar tip aneurysm clipping were imaged using real-time surgery angiography by ICG-VA, DIVA, ICG-VA with Flow 800 color mapping. These four cases are described as illustrative cases below. In the cerebral aneurysms and visualization of perforators by the endoscope, ICG-VA and DIVA were performed before and after clipping. In three cases, ICG-VA could not visualize perforators well compared to its better visualization by DIVA because of its deeper location and behind clips. In three cases, occlusion of perforators was seen on DIVA after clip application, which was solved by reapplication of the aneurysm clips. In the case of STA-MCA bypass surgery, patency and blood inflow sequences to the MCA cortical branches (M4) from recently anastomosed STA branches were assessed by ICG-VA DIVA as well as Flow 800 color mapping. All three were successful in revealing the flow and patency. These were also used in two cases of carotid endarterectomy proximal to CCA bifurcation to visualize the lack of blood flow and fluttering atherosclerotic plaques within the level of stenosis before the procedure. During surgery, the atherosclerotic plaque was dissected. It restored blood flow in the vessel which was confirmed by the imaging methods (ICG-VA, DIVA and Flow 800) as mentioned above and revealed a significant increase in blood flow (Figure 5).

3.1. Illustrative case 1

Left anterior choroidal artery aneurysm was found incidentally in 65 years old female patient. A left pterional transsylvian approach was performed to clip the aneurysm. To achieve successful aneurysm clipping, ICG-VA and DIVA were used to visualize blood flow during surgery. Intraoperative findings (Figure 1) within microscopic visualization show aneurysm of left internal carotid artery (ICA) anterior choroidal artery (white arrows) aneurysm, optic nerve (ON), posterior communicating artery, oculomotor nerve (OcN), dura, temporal and frontal lobes. The aneurysm sac was adherent to the temporal lobe and compressed the oculomotor nerve slightly. DIVA was then performed where blood flow within vascular structure appeared in green colour whereas surrounding structures' colours remained unchanged. ICG-VA was also used following DIVA to visualize blood flow within the aneurysm sac. It was clear from ICG-VA that the appearance of vascular structure in white within an almost complete black background where surrounding structures such as optic nerve, oculomotor nerve, dura, frontal and temporal lobes differentiation was impossible. After confirmation of blood flow within the aneurysm sac and internal carotid artery and other branches, the first clip was applied (Figure 1(d)), DIVA (Figure 1(e)) was used again to confirm aneurysm sac complete occlusion by clip where no part of the aneurysm was in green colour compared to the green coloured internal carotid artery, posterior communicating artery, and internal carotid artery's bifurcation forming anterior cerebral artery (A1) and middle cerebral artery (M1). The green colour of the anterior choroidal artery and its branches signified that the small perforators were not occluded by the clip.

Next to DIVA, ICG-VA (Figure 1(f)) is also used for the same purpose as DIVA. On the screen where during ICG-VA, blood flow within aneurysm was determined and appeared in white (yellow arrow and border circle shape yellow line). ICG-VA also confirmed it saved the anterior choroidal artery coloured in white (red arrows). This incomplete aneurysm occlusion problem

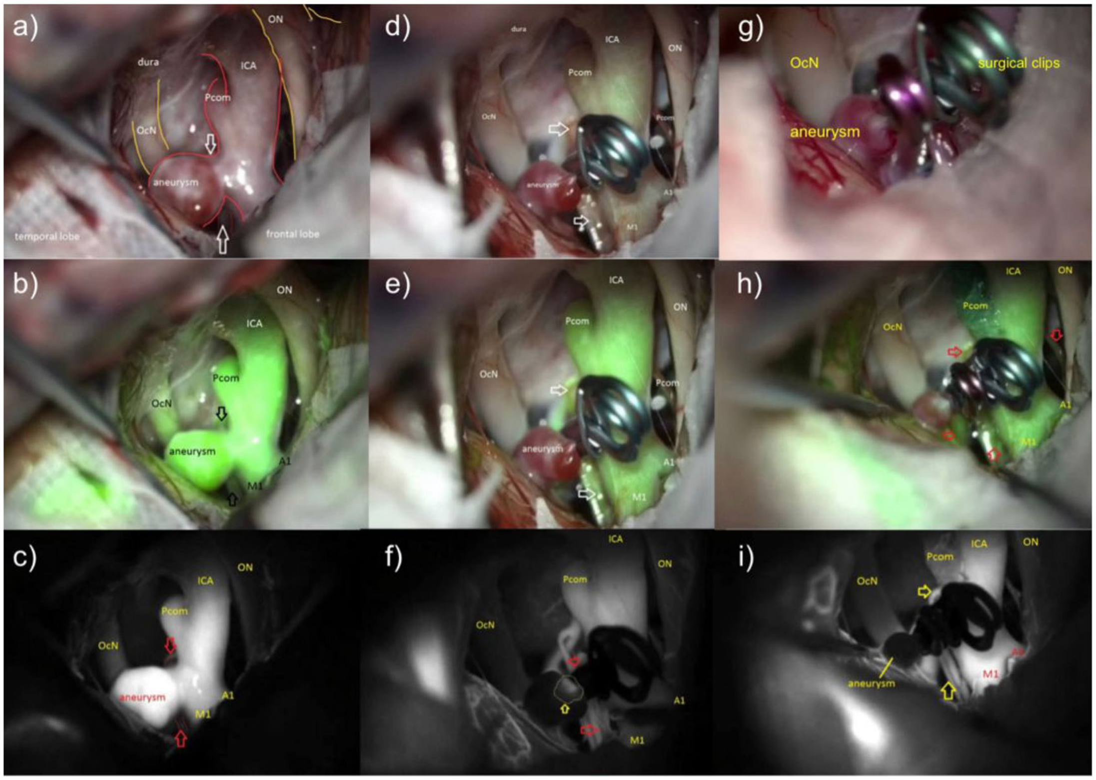


Figure 1. Intraoperative visualizations of left IC anterior choroidal artery aneurysm (ICA-internal carotid artery, OcN-oculomotor nerve, ON-optic nerve, Pcom-posterior communicating artery, arrow-anterior choroidal arteries). a- aneurysm and surrounding structures in the original view of the surgical field. b-Dual image video angiography (DIVA) of the same surgical area, c-Indocyanine green video angiography (ICG-VA) of the same surgical field. d-first clip application, e-DIVA image after first clip, f-ICG-VA after the first clip (the yellow circle-shaped area surrounding the white background reveals blood flow within the aneurysm, the second clip was applied (g) and complete occlusion of aneurysm confirmed by DIVA (h) and ICG-VA (i).

was solved by applying the second clip (Figure 1(g)). DIVA (Figure 1(h)) and ICG-VA (Figure 1(i)) were also performed to confirm total aneurysm sac occlusion. On both DIVA and ICG-VA, saved perforators (yellow arrows, Figure 1(h) and (i)) were seen. The postoperative period was without complication.

3.2. Illustrative case 2

A 64-year-old male was admitted after finding a right cervical ICA stenosis that approximates the foramen lacerum on CTA. Right STA-MCA (M4 segment) bypass was performed, and real-time surgery ICG-VA, DIVA, and ICG-VA with Flow 800 were used to visualize vascular and surrounding structures. Intraoperative visualization within the microscopic field (Figure 2(a)) illustrated right STA-MCA bypass (black arrow), cerebral cortex (yellow asterisk), cortical veins (yellow arrow), and arteries (green arrow) were seen in the original color, which appeared as the white color within the black background on ICG-VA performed alone (Figure 2(b)). Intraoperative DIVA confirmed blood flow throughout the first STA-MCA bypass (yellow circle). The STA branch was covered by fat, and its original fascia-specific green color on DIVA was not clear (Figure 2(c)). However, arteries, veins, and cortical small arterial vessels appeared in a different Flow 800 color-coded map (Figure 2(d)) where STA and cortical segments of right middle cerebral arteries appeared in red, veins are in blue, and small arterial cortical vessels are in yellow. Single STA-MCA bypass could not compensate for insufficient blood circulation within left-right MCA. Therefore, the second STA-MCA bypass with another STA branch and MCA M4 segment was performed (Figure 2(e)). A significant improvement in blood flow appeared on ICG-VA; there were more vascular structures (Figure 2(f)) than vascular structures that appeared on previous ICG-VA. A similar appearance was seen in both DIVA (Figure 2(g)) and Flow 800 color-coded map (Figure 2(k)). The critical point is that vascular structures that appeared in a different color on the second Flow 800 color-coded (Figure 2(k)) were more than other colored vascular systems on the previous Flow 800 map proving that sufficient blood circulation was achieved. On the postoperative day of one, CTA was performed to confirm the functioning donor STA (Figure 3. arrows).

3.3. Illustrative case 3

A seventy-four-year-old male was admitted with transient headache and right-side weakness. Preoperative CTA showed left carotid artery (CA) stenosis. Carotid endarterectomy was performed. During surgery yellow colored atherosclerotic plaque (black asterisk) was seen within the surgical field of the microscope (Figure 4(a)). That atherosclerotic plaque appeared as a black spot within ICG-VA's white color on a black background (Figure 4(b)). We performed midline arteriotomy and removed fluttering atherosclerotic plaque, which narrowed the carotid artery. After suturing, DIVA (Figure 4(d)), ICG-VA (Figure 4(e)) and ICG-VA with Flow 800 were performed revealing removal of atherosclerotic plaque, which was seen as the disappearance of the black spot on DIVA and ICG-VA (Figure 4(d,e), red asterisk). Flow 800 color-coded map (Figure 4(f)) showed the disappearance of atherosclerotic plaque as increased blood flow in red color).

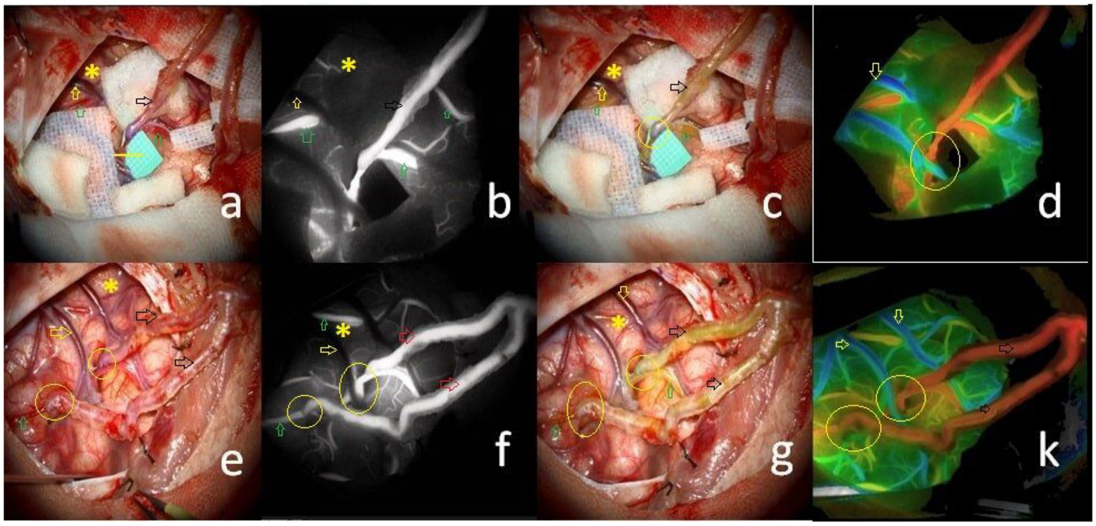


Figure 2. Intraoperative visualization of STA-MCA bypass with use of ICG-VA, DICA and ICG-VA with Flow 800 color-coded map. "a" and "e"- view of the surgical field under the microscope where the black arrow is the frontal branch of right STA, yellow asterixis brain cortex, yellow arrow-cortical veins, green arrows are arteries. "b" and "f"- vascular structure's appearance within ICG-VA in which all vascular structures marked with different symbols before appeared as the white color within the only black background. "c" and "g" illustrates DIVA, "d" and "k" – Flow 800 color-coded map where vascular structures such as arteries, small arterial cortical vessels, and cortical veins appeared in a different color; red, yellow and blue respectively.

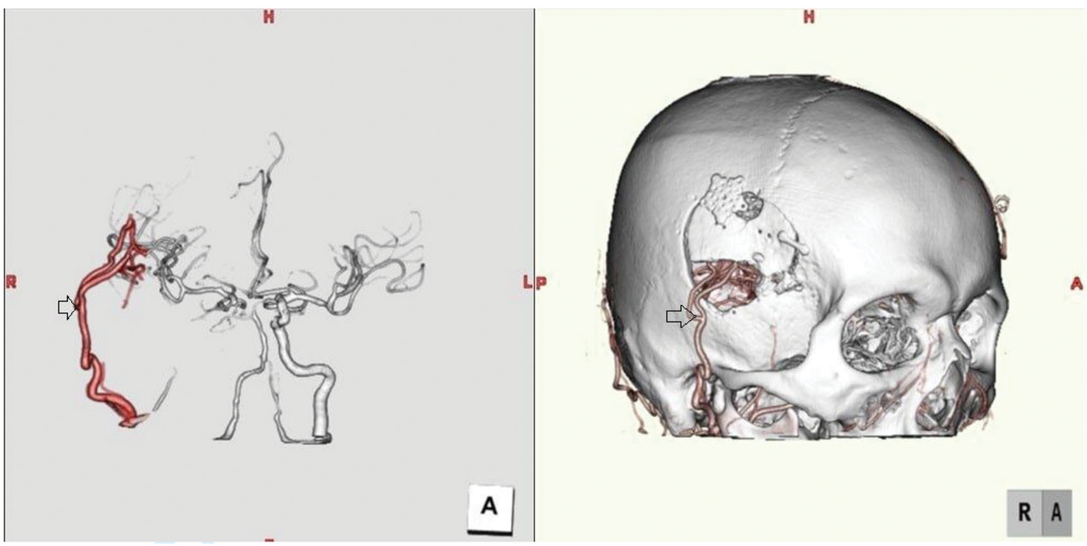


Figure 3. Postoperative 3D STA of functioning STA-MCA bypass (arrow).

3.4. Illustrative case 4

A 68-year-old female with incidentally found basilar tip aneurysm on CTA (Figure 5 (A and B) in red arrows) underwent surgery via right pterional transsylvian approach (Figure 5(B)) for aneurysm clipping. Intraoperative findings confirmed and matched preoperative CTA (Figure 6). To visualize blood flow within the microscopic field, ICG-VA with Flow 800 was used, and color-coded map and intensity diagrams were made before (Figure 7(A)) and after clipping (Figure 7(B)). On the color map and intensity diagram, it was clear that Flow 800 was less than 1 minute (52 sec) and relative intensity within aneurysm was 65% before clipping, which was marked with red color on the diagram and color map. Regions of interests (Aneurysm, ipsilateral and contralateral posterior communicating artery –P1 marked with red, blue, and green color respectively) data such as time delay, speed, time to peak, and rise time is also shown on the same image. The intensity diagram and color-coded map after clipping revealed no flow within aneurysm sac marked with a red line and significant increase of intensity within both P1 marked with a blue and red line (Figure 7(B)).

4. Discussion

Intraoperative angiography techniques such as ICG-AG and DIVA are effective methods for the assessment of vascular surgery techniques. Initially, ICG usage was focused on hepatic diseases, later on cardiology, and recently on cancer treatment.[7,8] In mid-1968, the first successful ICG-AG for intracranial vessels was performed by Earl and Kogure on owl monkeys and then attempted on volunteers with no success.[9] ICG-VA can visualize a clear and intraoperative vascular image during microsurgical procedures such as incomplete clipping. Patients with unruptured aneurysms can also be assessed with ICG-VA.[10] Furthermore, the indocyanine green has been used to delineate the internal carotid artery during endoscopic endonasal transsphenoidal surgery.[11] However, it might not visualize surrounding structures other

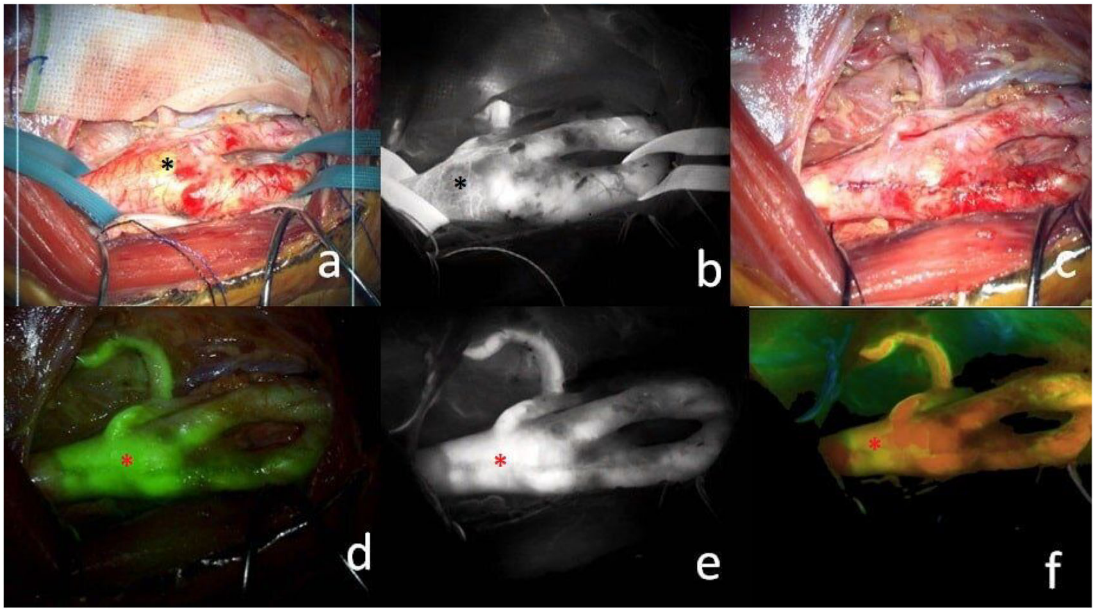


Figure 4. Intraoperative ICG-VA, DIVA, and ICG-VA with Flow 800 visualization of carotid endarterectomy.

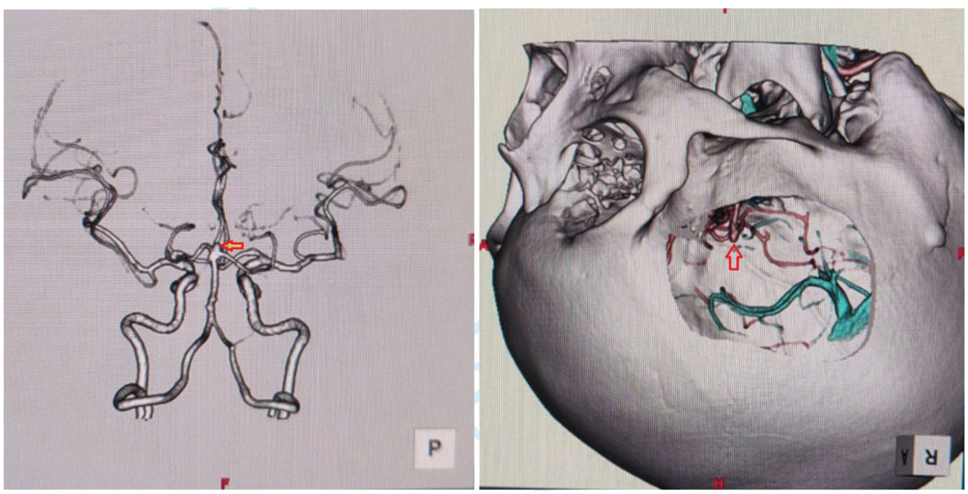


Figure 5. From left to right; Preoperative 3D CTA shows the basilar tip aneurysm (red arrows) and surgical approach (right pterional transsyvian approach).

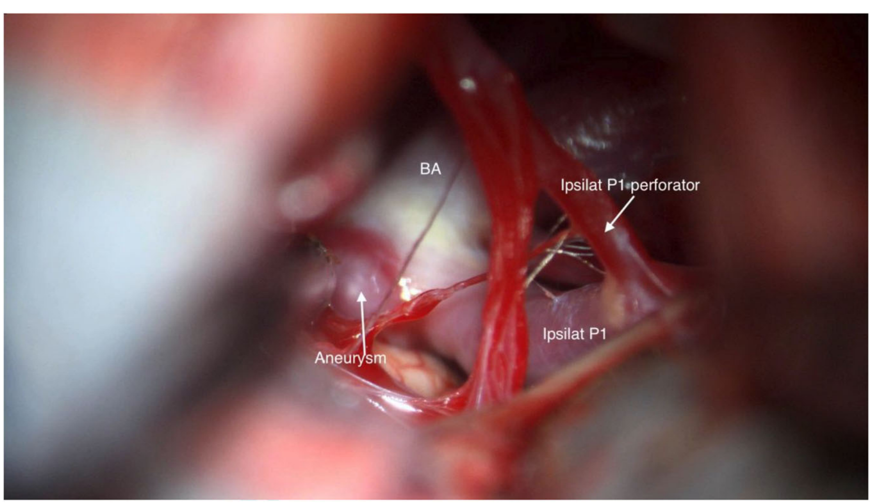
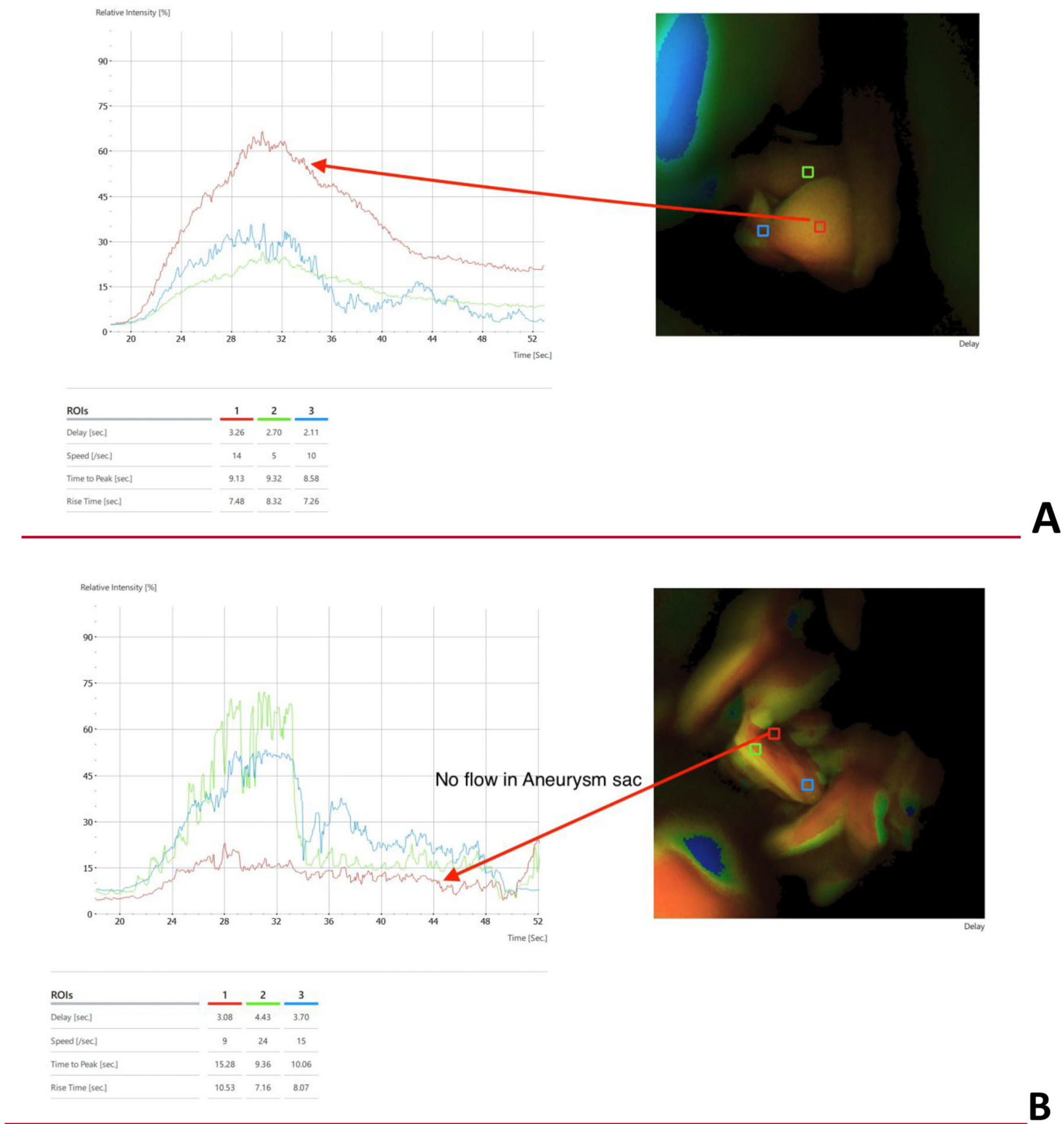


Figure 6. Visualization of basilar tip aneurysm along with other vascular structures; basilar artery (BA), ipsilateral P1 and its perforators.



ROIs	1	2	3
Delay [sec.]	3.26	2.70	2.11
Speed [/sec.]	14	5	10
Time to Peak [sec.]	9.13	9.32	8.58
Rise Time [sec.]	7.48	8.32	7.26

ROIs	1	2	3
Delay [sec.]	3.08	4.43	3.70
Speed [/sec.]	9	24	15
Time to Peak [sec.]	15.28	9.36	10.06
Rise Time [sec.]	10.53	7.16	8.07

Figure 7. Flow 800 intensity diagram before (A) and after (B) aneurysm clipping.

than NIR fluorescence white-colored vessels in the dark background field. This problem was solved by realizing a fluorescence angiography with augmented microscopy enhancement on animal studies.[12] It also proved that it enables green-fluorescent NIR images to be superimposed on the white light anatomical field. This technique helped to identify small vessels covered with a thin connective tissue layer. Sato *et al.*[13] reported a similar case developing dual image video angiography, a novel tool to observe surrounding structures. DIVA made the most challenging neurovascular procedures possible and practical because it gives vessels colored green during altered dynamic of blood flow after ICG dye injection. DIVA has some benefits compared to ICG-AG as it helps visualize the surrounding structures, nerve, aneurysm clips, deeply located perforators and parent vessels while ICG-AG does not. In ruptured micro-AVMs, ICG-VA usage confirms AV shunts, especially in AVMs with superficial drainage, and has been reported by many authors as safe and effective.[14] However, both ICG-VA and DIVA provide only anatomical data without information about blood flow's physiology and dynamics. The Flow 800 imaging produces intensity diagrams and color mapping. Image analysis with software is a package to distinguish the physical properties of the flow in vessels and demonstrate semi-quantitative data for tackling the problems.[15] Notable, it is useful to visualize the feeding arteries of Spetzler-Martin Grade IV arteriovenous malformation. The subsequent intensity diagram and a colour map of flow 800 facilitated AVM vessels' distinction, namely, feeding arteries, draining veins, and arterialized veins from other normal vessels, such as arteries *en passage.*[16] ICG-VA was also reported to detect fluttering atheroma in the extracranial arteries.[17] During ICG Video angiography, the original NL camera and new NIR system were used to detect anatomical and fluorescence signals. The New NIR system enabled observation of ICG fluorescence and anatomical structures without image fusion or time-delay.[18]

In our study, both ICG-VA and DIVA and ICG-VA with Flow 800 were used to visualize surrounding structures within the surgical field of the microscope and proved useful in our surgical procedures, and the distinction of arterial-venous circulation was also valuable. In IC anterior choroidal artery aneurysm surgery, during dual-image video angiography (DIVA), despite green coloured aneurysm and other vascular structures (Figure 1), surrounding structures such as optic nerve, oculomotor nerve, dura, and brain cortex appeared with their original colour in the surgical field. In contrast, during ICG-VA of the same structures within surgical view, aneurysm and other vascular structures like Internal carotid artery (IC), posterior communicating artery (Pcom), anterior choroidal artery appeared as white in the black background. Surrounding structures were almost invisible during ICG-VA. Similar images were also seen in illustrative case 2, where ICG-VA illustrated white-coloured vessels without structural differentiation within black background only. However, when ICG-VA with Flow 800 was performed, better differentiation of vascular structure (arteries-red, small arterial vessels-yellow and veins-blue) was achieved. The intensity diagram of Flow 800 showed excellent aneurysm clipping.

Limitations of study

Due to a small number of patients selected for this study, a detailed evaluation of the technical aspects regarding the utility of intraoperative video angiography techniques based on the use of ICG was conducted. To achieve better results about the priorities of this technique more data and large case series or some multicenter studies needed to be carried out.

5. Conclusion

1. Dual image video angiography has a superiority over the ICG-AG. It gives better visualization of the vessels amongst other surrounding structures due to the visibility of the brain cortex, cranial nerves, and clip position in aneurysm surgery.
2. Determining region of interest, intensity diagram, and color mapping of Flow 800 usage combined with conventional ICG-VA outweighs benefits over the ICG-AG performed alone and DIVA.
3. Use of ICG-VA in all modalities, as mentioned earlier, proves that ICG-VA remains an essential method of intraoperative visualization of the human brain's vascular structures.

ICG techniques are widely being used in many centers, because it is simple and safe and we can get faster results with high-resolution real-time images. They produce the direction and relative magnitude of flow to and from vascular lesions for surgeon, which can be used to evaluate the patency of the parent artery, branch artery, and bypass artery to change the decision during surgery. However, the information is subjective and needs to be judged by surgeons with rich experience as this is only an evaluation of the technical aspect regarding the utility of the technique.

Author contributions

Khabibullo A. Khasanov, Gulnara A. Alikhodjayeva, Kaan Yagmurlu and Bipin Chaurasia have given substantial contributions to the conception of the design of the manuscript. Author Yasuhiro Yamada and Khabibullo Khasanov, Jakhongir B.Yakubov collected images and its interpretation. Yasuhiro Yamada and Yoko Kato performed surgeries. All authors read and approved the final version of the manuscript. All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

Disclosure statement

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ORCID

Bipin Chaurasia http://orcid.org/0000-0002-8392-2072

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