

Development of and Clinical Experience with a Simple Device for Performing Intraoperative Fluorescein Fluorescence Cerebral Angiography: Technical Notes

Tsuyoshi ICHIKAWA,¹ Kyouchi SUZUKI,¹ Yoichi WATANABE,¹ Taku SATO,²
Jun SAKUMA,² and Kiyoshi SAITO²

¹*Department of Neurosurgery, Fukushima Red Cross Hospital, Fukushima;*

²*Department of Neurosurgery, Fukushima Medical University, Fukushima*

Abstract

To perform intraoperative fluorescence angiography (FAG) under a microscope without an integrated FAG function with reasonable cost and sufficient quality for evaluation, we made a small and easy to use device for fluorescein FAG (FAG filter). We investigated the practical use of this FAG filter during aneurysm surgery, revascularization surgery, and brain tumor surgery. The FAG filter consists of two types of filters: an excitatory filter and a barrier filter. The excitatory filter excludes all wavelengths except for blue light and the barrier filter passes long waves except for blue light. By adding this FAG filter to a microscope without an integrated FAG function, light from the microscope illuminating the surgical field becomes blue, which is blocked by the barrier filter. We put the FAG filter on the objective lens of the operating microscope correctly and fluorescein sodium was injected intravenously or intra-arterially. Fluorescence (green light) from vessels in the surgical field and the dyed tumor were clearly observed through the microscope and recorded by a memory device. This method was easy and could be performed in a short time (about 10 seconds). Blood flow of small vessels deep in the surgical field could be observed. Blood flow stagnation could be evaluated. However, images from this method were inferior to those obtained by currently commercially available microscopes with an integrated FAG function. In brain tumor surgery, a stained tumor on the brain surface could be observed using this method. FAG could be performed with a microscope without an integrated FAG function easily with only this FAG filter.

Key words: aneurysm surgery, fluorescence angiography, fluorescein sodium, ischemic complication

Introduction

Fluorescence angiography (FAG) has been used to confirm the patency of the parent artery, perforating artery, and other arteries that branch near an aneurysm during aneurysm surgery.^{1–8)} FAG has also been used during excision of brain tumors to identify tumor margins⁹⁾ and confirm the patency of the blood vessels around the tumor.¹⁰⁾ Since FAG is minimally invasive and useful for decreasing the incidence of surgical complications, FAG is widely used during neurological surgery. However, commercially available microscopy systems that can support FAG require additional infrared camera since indocyanine green (ICG) is used as dye. Therefore, it is not easy to purchase the equipment for performing FAG due to its high price.

We made a device (FAG filter; Scimen Design Ltd., Tokyo) for easily performing intraoperative FAG using a microscope without an integrated FAG function that is reasonably priced, easy to use, and has enough quality for evaluation. The FAG filter is a small, light device that can easily be held in one hand. Both the exciting light and the fluorescence of fluorescein are in a visible range. Therefore by using fluorescein as a reagent in this method, additional special equipment such as the infrared camera is not necessary. We investigated the practical use of this device for confirming the patency of arteries, capillaries, and veins in the surgical field and identifying dyed brain tumors.

Materials and Methods

Clinically, indocyanine green and fluorescein sodium are dyes used in FAG. For FAG using the FAG filter, fluorescein sodium was used. When excited by blue

light, fluorescein sodium emits green light. After administration of an intravenous or intra-arterial bolus injection of fluorescein sodium (Fluorescite®, Alcon Japan Co., Tokyo), the crescendo of fluorescence was observed under the microscope through the FAG filter.

There are three holes in the FAG filter. One hole is for light from the microscope's light source to pass through; this hole is covered with an excitatory filter. The other two holes are for observing the surgical field, which are covered with barrier filters (Fig. 1A–D). The excitatory filter excludes all wavelengths except for blue light and the barrier filters are long-pass (blue cut) filters; the wavelength at the half-transmittance point is approximately 500 nm. There are also three holes in the bottom of the surgical microscope cylinder. One hole is for light from the microscope's light source to pass through and the other two holes are for observing the surgical field (Fig. 2A). The FAG filter was designed to be placed in same position as the three holes of the microscope (Fig. 2B, C). The FAG filter is hand-held in the appropriate position at the bottom of the surgical microscope cylinder. The FAG filter could be installed in the appropriate location easily within 10 seconds.

The surgical field is illuminated by white light from the surgical microscope's light source, which contains all wavelengths (Fig. 3A). By adding this FAG filter to the microscope, white light from the microscope

becomes blue light that illuminates the surgical field (Fig. 3B). The lights in the operating room are turned off, so that only the surgical field is illuminated with blue light (Fig. 3C). At this point, an intravascular bolus injection of fluorescein sodium is delivered and fluorescence from the blood vessels in the surgical field is visible. Blue light from the surgical field is blocked by the barrier filter, so that the crescendo of fluorescence is observed through the microscope directly and recorded by a memory device (Fig. 3D).

The operator can directly observe stagnation, delay, and direction of blood flow with FAG. In addition, we constructed a graph of fluorescence emission intensity in the arteries, capillaries, and veins using fluorescence analysis software (Hamamatsu Photonics, Tokyo).

The study sample consisted of patients with intracranial aneurysm ($n = 12$), superficial temporal artery (STA), middle cerebral artery (MCA) anastomosis ($n = 2$), or brain tumor ($n = 4$); all underwent intraoperative fluorescein cerebral angiography. Aneurysms were located in the internal carotid ($n = 5$), middle cerebral ($n = 6$), and anterior communicating arteries ($n = 1$). Pathology of brain tumors consisted of meningioma ($n = 2$), low-grade astrocytoma ($n = 1$), and metastatic brain tumor ($n = 1$). M500OHS-1 (Leica, Wetzlar, Germany) was used as the microscope system.

The local ethics committee approved this study, and all patients provided written informed consent

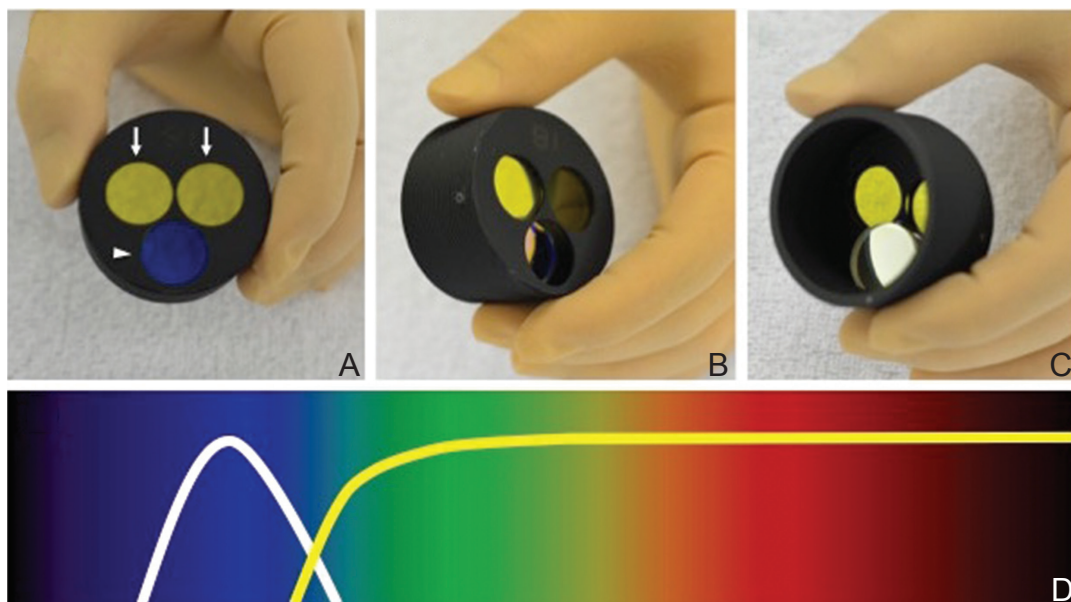


Fig. 1 The FAG filter: front view (A), anterior oblique view (B), and posterior oblique view (C). The FAG filter consists of two types of filters. One is an excitatory filter (*white arrowhead*) and the other is a barrier filter (*white arrows*). The excitatory filter excludes all wavelengths except for blue light (D: *white line*) and the barrier filter passes long wavelengths, except for blue light (D: *yellow line*). FAG: fluorescence angiography.

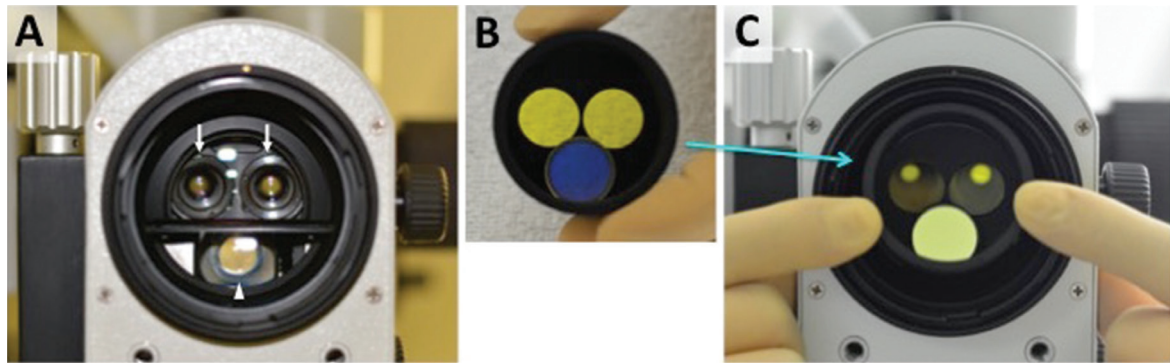


Fig. 2 There are three holes in the bottom of the surgical microscope cylinder (A). One hole is for the light from the microscope's light source to pass (*white arrowhead*) and the other two holes are for observation of the surgical field (*white arrows*). The FAG filter is positioned at the bottom of the surgical microscope cylinder so that the light from the microscope's light source may pass through the FAG filter's excitatory filter and the operator may observe the surgical field through the barrier filter (B, C). The FAG filter is held in contact with the objective lens. FAG: fluorescence angiography.

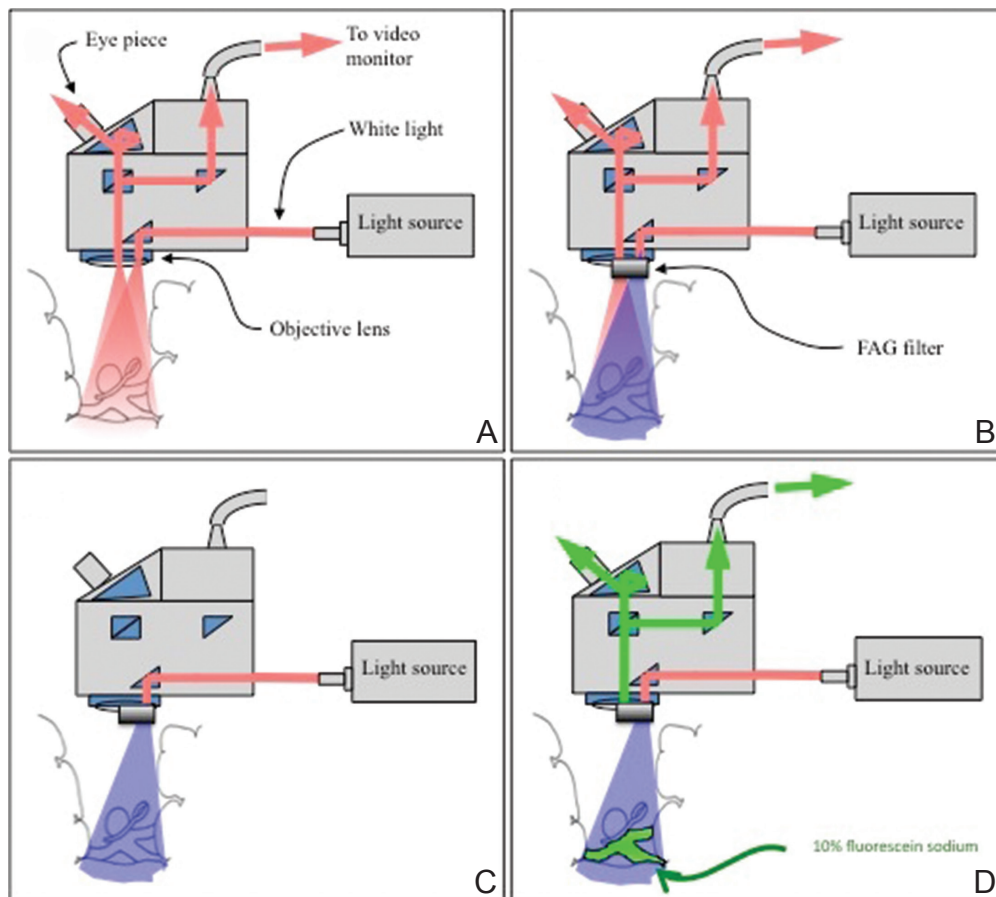


Fig. 3 Drawing showing the setup for intraoperative FAG using the FAG filter. A: White light containing all wavelengths is emitted from the surgical microscope's light source. B: By adding the FAG filter to the microscope, white light from the microscope becomes blue light that illuminates the surgical field. C: The lights in the operating room are turned off, and only the surgical field is illuminated by blue light. D: Next, an intravenous bolus injection of fluorescein sodium is delivered and fluorescence from the vessels appears in the surgical field. Blue light from the surgical field is blocked by the barrier filter, so that the crescendo of fluorescence is observed through the microscope directly and is recorded by a digital video camera.

forms for performing intraoperative videoangiography with fluorescein sodium dye.

Results

Compared to the original image, the surgical field was dimmer after the FAG filter was attached to the microscope, but it remained sufficiently illuminated to proceed with surgical manipulations. Approximately 20 seconds after the delivery of 5 ml of a 10% fluorescein sodium bolus via a peripheral venous line, fluorescence in the vessels was clearly observed through the microscope and recorded on the memory device. Both the major cerebral arteries (3 mm in diameter) and perforating arteries (0.5 mm in diameter) became yellowish-green. Fluorescence from arterioles (approximately 0.1 mm in diameter) on the brain surface could also be identified very clearly. In cases that needed repeated FAG, intra-arterial injection of fluorescein was performed because of quick clearance of fluorescence. To reduce risk of examination, catheter was inserted from the superficial temporal artery.³⁾ It was difficult to observe fluorescence from a thickened or calcified major artery, such as the internal carotid artery (ICA), mostly because the amount of excitation and fluorescence was attenuated when the light passed through the thick arterial walls.

After aneurysm clipping, good image quality and spatial resolution facilitated intraoperative real-time assessment of the patency of the patent artery, perforating arteries, and other arteries that branch near the aneurysm. After STA-MCA anastomosis, the patency of the anastomosis was confirmed. In addition, a graph of fluorescence intensity in the arteries, capillaries, and veins made with fluorescence analysis software made independent peak and we evaluated whether blood flow was sufficient. During brain tumor surgery, excellent fluorescence images were observed in two cases (meningioma: 1, metastatic brain tumor: 1), and no fluorescence images could be obtained in the other two cases (meningioma: 1, low-grade astrocytoma: 1). All 18 patients experienced an uneventful postoperative course without clinical complications. There were no complications attributable to fluorescein sodium injection.

I. Illustrative case 1

A 72-year-old woman underwent neck clipping of a large unruptured right MCA (17 mm) aneurysm. After right frontotemporal craniotomy, the Sylvian fissure was opened and the large aneurysm was exposed. The wall of the aneurysm near the neck was sclerotic and thickened (Fig. 4A). FAG with intra-arterial injection of fluorescein sodium via the

superficial temporal artery was performed. Fluorescence from parent arteries was identified very clearly, with blood flow swirling within the aneurysm (Fig. 4B). The M1 portion of the MCA was temporarily clipped and the first clip was placed on the aneurysmal neck parallel to M2 of the MCA. However, a single clip did not totally obliterate the aneurysm due to the thick aneurysmal wall near the neck. A second clip was then applied parallel to the first clip distally. The inferior trunk of M2 appeared bent and collapsed (Fig. 4C); therefore, FAG using the FAG filter was performed. The fluorescence from the inferior trunk of M2 was not observed (Fig. 4D). The first clip was removed and applied parallel to the second clip more distally. After this manipulation, blood

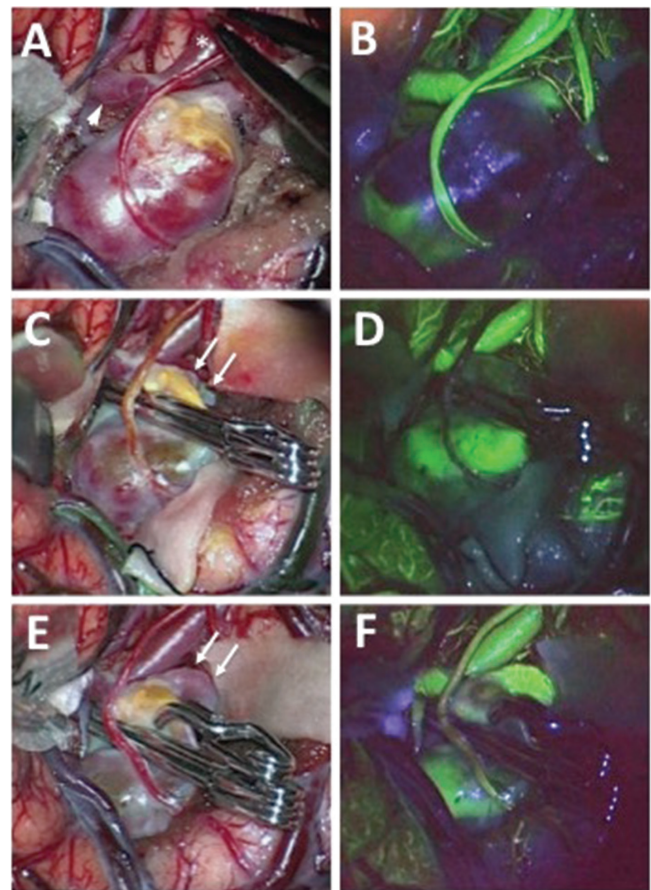


Fig. 4 Case 1: Large, unruptured right MCA (17 mm) aneurysm. The wall of the aneurysm was sclerotic and thickened (A, B). Two clips were placed on the neck. The inferior trunk of M2 (*white arrow*) seemed bent (C) and fluorescence from the inferior trunk of M2 could not be observed (D). The aneurysm was obliterated with three clips (E) and fluorescence from the inferior trunk of M2 (*arrow*) and other vessels in the surgical field could be identified (F). *White asterisk*: M1 portion of MCA, *arrowhead*: superior trunk of M2, MCA: middle cerebral artery.

flow in the inferior trunk of M2 was confirmed by the Doppler ultrasonography but MEP disappeared. Therefore, the second clip was re-applied more distal to the first clip. A third clip was applied on the residual dome near the aneurysmal neck (Fig. 4E). Fluorescence from the inferior trunk of M2 and other vessels in the surgical field appeared normal (Fig. 4F). Subsequently, MEP recovered to baseline levels. In this case, repeated FAG could be done by intra-arterial injection. There was transient postoperative left hemiparesis that resolved within 24 hours. Postoperative magnetic resonance imaging (MRI) showed no ischemic lesions and the patient was discharged without any neurological deficits.

II. Illustrative case 2

A 68-year-old woman experienced a transient ischemic attack secondary to right ICA occlusion. The STA was anastomosed to the M3 portion of the MCA (Fig. 5A). To confirm the patency of the anastomosis, FAG using the FAG filter was performed. After intravenous injection of fluorescein sodium,

fluorescence from the arterioles on the surface of the brain supplied by the recipient artery was clearly observed first (Fig. 5B), and fluorescence from the surrounding brain surface was observed after a few seconds (Fig. 5C). When the regions of interest (ROIs) were set at the recipient artery, surrounding artery, and their supplied brain surface, the pixel intensity curve of the brain surface supplied by the recipient artery rose first, and the curve for the surrounding brain surface rose approximately 2 seconds later (Fig. 5D). Postoperative MRI showed no new lesions and the patient was discharged without any neurological deficits.

III. Illustrative case 3

A 48-year-old woman underwent neck clipping of a ruptured left ICA posterior communicating artery junction aneurysm via a standard frontotemporal craniotomy. After clipping (Fig. 6A), FAG was performed to confirm blood flow in the anterior choroidal and posterior communicating arteries. Emission from the ICA, anterior choroidal artery,

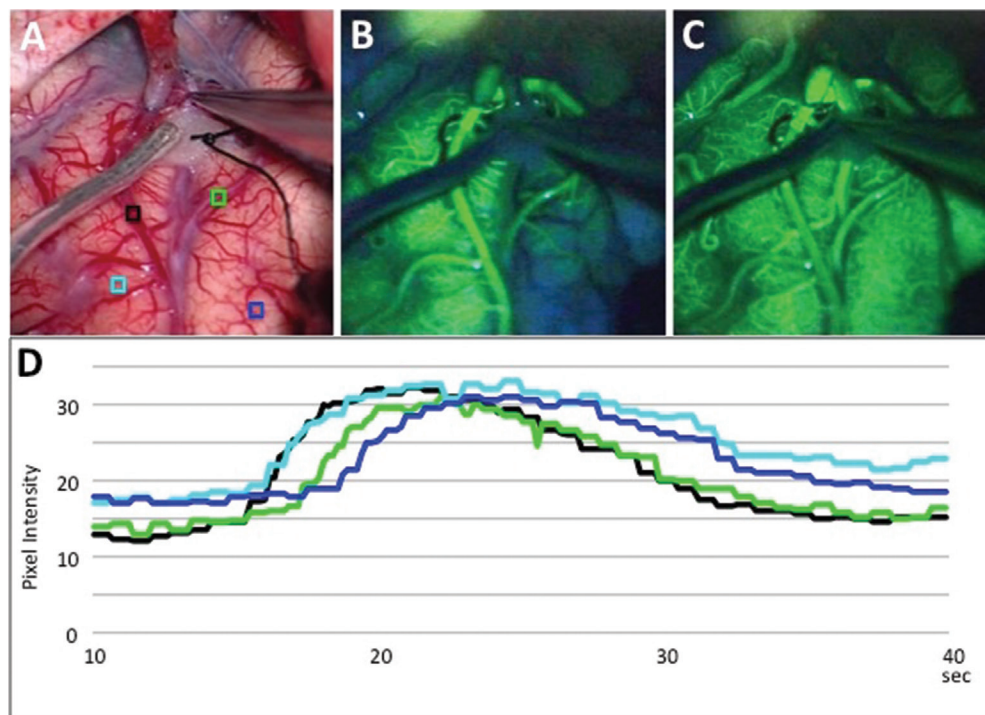


Fig. 5 Case 2: A: The superficial temporal artery (STA: *white arrow*) was anastomosed to the M3 portion (*arrowhead*) of the middle cerebral artery. B: After intravenous injection of fluorescein sodium, fluorescence from the arterioles on the brain surface supplied by the recipient artery was clearly observed, C: fluorescence from the surrounding brain surface was observed a few seconds later. It seemed that the excitation light illuminated the surgical field uniformly and at a constant intensity. Regions of interest (ROIs) were set at the recipient artery and the brain surface it supplies (*black and light blue open squares*), and the surrounding artery and brain surface (*green and blue open squares*). Changes in the intensity of fluorescence at each ROI were plotted. The pixel intensity curve of the brain surface supplied by the recipient artery increased first, and the curve of the surrounding brain surface increased approximately 2 seconds later.

and posterior communicating artery were clearly observed through the microscope (Fig. 6B).

IV. Illustrative case 4

A 62-year-old man presented with left visual dysfunction. MRI demonstrated a tuberculum sellae meningioma. Surgery was performed via a

right frontotemporal craniotomy. Before manipulation of the tumor, FAG using the FAG filter was performed. Fluorescence from the tumor, pituitary stalk, anterior cerebral artery, and arterioles on the right optic nerve were clearly observed (Fig. 7A, B). After tumor removal, we confirmed that the tumor was totally removed and the arterioles on the right

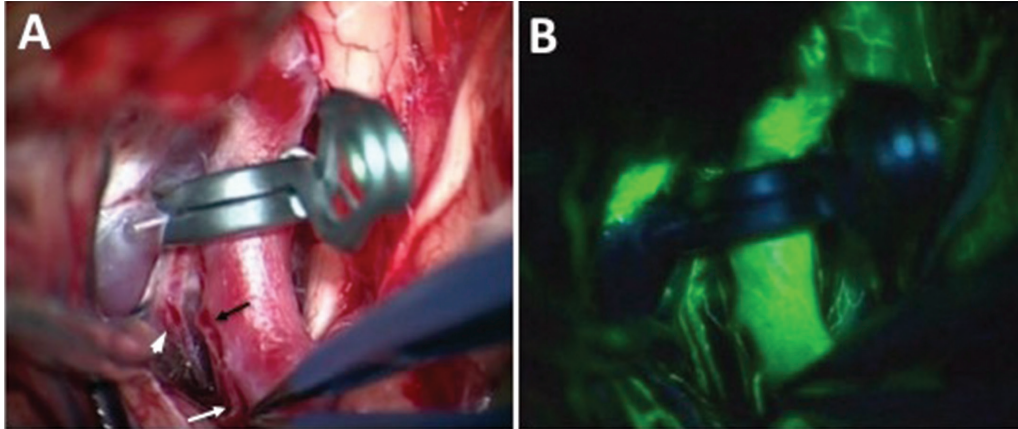


Fig. 6 Case 3: Intraoperative regular microscopic view (A) and arterial phase of fluorescence angiography (B). After clipping, the patency of the posterior communication artery (*white arrowhead*), anterior choroidal artery (*black arrow*), and direct perforating artery from the internal carotid artery (*white arrow*), and arteriole on the optic nerve, respectively, were confirmed using fluorescence cerebral angiography.

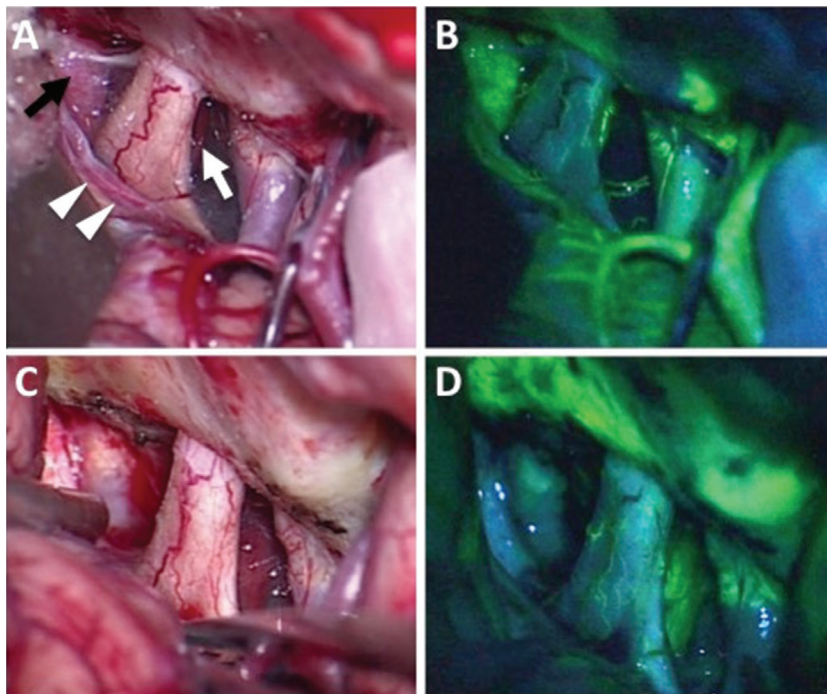


Fig. 7 Case 4: Before tumor resection (A, B), fluorescence within the tumor (*arrow*), A1 segment of the anterior cerebral artery (*white arrowheads*), pituitary stalk (*white arrow*), and arterioles on the optic nerve were observed by fluorescence angiography. After tumor resection (C, D), total excision of the tumor and the lack of vascular damage in the surgical field were confirmed.

optic nerve were intact (Fig. 7C, D). Left visual function recovered postoperatively, and the patient was discharged without any neurological deficits.

Discussion

To detect insufficient blood flow in parent arteries and perforators during aneurysm surgery, Doppler ultrasonography,¹¹⁾ conventional cerebral angiography,¹²⁾ endoscopic observation,¹³⁾ and electrophysiological monitoring^{14–17)} have been used and modified. Even with the use of these multiple modalities, unexpected ischemic complications might occur.^{18,19)} To avoid these complications, FAG has been used. FAG might be of great help in preventing blood flow insufficiency of perforating arteries that cause severe dysfunction and cannot be monitored so far, such as hypothalamic artery.²⁰⁾

FAG was first used in neurosurgery in 1967 when Feindel et al.^{21,22)} injected fluorescein sodium into the carotid artery and observed blood flow in the cortical vessels. In 1994, Wrobel et al.²³⁾ injected fluorescein intravenously and observed blood flow in the parent artery during aneurysm surgery, but it was difficult to procure images due to weak illumination and poor imaging technology at that time. In 2001, Kuroiwa et al.⁹⁾ reported the usefulness of intraoperative FAG with a microscopy system that has an integrated FAG function. In 2005, Raabe et al.⁷⁾ observed blood flow through perforators deep in the surgical field using a microscopy system with an integrated high-power light unit. In 2007 Suzuki et al.²³⁾ reported that FAG with fluorescein could detect insufficient blood flow through perforators deep in the surgical field. Currently, there are commercially available microscopy systems such as the Carl Zeiss OPMI Pentero 900 that can support FAG with both ICG and fluorescein. In 2013 Rey-Dios and Cohen-Gadol⁸⁾ reported on the usefulness of FAG using fluorescein sodium with the OPMI Pentero 900 microscopy system. In addition to intracranial aneurysm surgery, FAG has also been used in brain tumor surgery to identify tumor margins and in revascularization surgery.

FAG has been accepted as a surgical support technique. However, some challenges remain. Not every hospital or department can purchase the equipment because it is expensive. To solve this problem, we made a small and simple device to perform fluorescein FAG, the FAG filter, and investigated the practical use of this device. It is possible to confirm the patency of the small perforating arteries deep in the surgical field and to identify margins of brain tumors even with a microscope without an integrated FAG function using our FAG filter.

Fluorescence images could be observed through the microscope directly and recorded in a memory device. In this study, although vessels with thin walls such as the M2 portion of the MCA and superficial vessels of the brain were clearly observed, arteries deep in the surgical field covered with blood or cerebrospinal fluid (CSF) and arteries with thick walls or calcifications such as the ICA could not be clearly observed.

The clarity of fluorescence images observed under a microscope with the FAG filter might slightly lower than those obtained using a commercially available microscope with an integrated FAG function. Inadequate FAG images may lead to misjudgments of blood flow insufficiency²⁴⁾ and unexpected postoperative ischemic complications. One challenge for the future is to further clarify the fluorescence especially from arteries with thick walls or covered by CSF.

It is important that the excitation light enter the surgical field uniformly and at a constant intensity. If the excitation light intensity is heterogeneous or fluctuating, the fluorescence in the surgical field also becomes heterogeneous or fluctuating. In this situation, when the fluorescence is not visible, it is difficult to determine whether there is blood flow insufficiency. We made a graph of the fluorescence emission intensity at several points in the operative field using fluorescence analysis software. The graphs drawn each point were almost the same, confirming that the excitation light entered the surgical field uniformly and at a constant intensity.

The intraoperative fluorescein cerebral angiography results presented in this study can be obtained using any type of the operating microscope if the FAG filter is fitted. It is easy to hold the FAG filter beneath the microscope; modifications of the operating microscope are not necessary. The FAG filter would cost approximately 4,000 USD. With improvements in the performance of the filter, fluorescence images obtained can become clearer, but at the same time the cost of the FAG filter would increase. We considered the balance between cost and performance when designing this filter. If a low-price filter with high performance can be made, the resolution of the images obtained using the FAG filter could be improved. The FAG filter must be sterilized using EOG gas, not with autoclaving. The performance of the FAG filter was not reduced with 50 sterilization cycles.

Conclusion

To perform intraoperative FAG with a microscope that lacks an integrated FAG function that is reasonable in cost, easy to use, and with sufficient image

quality for evaluation, we made a novel device called the FAG filter. FAG with the FAG filter was easy and rapid. Blood flow of small vessels deep in the surgical field and stained tumors on the brain surface could be observed using this method. Blood flow stagnation could be evaluated since the whole surgical field was illuminated uniformly by the excitatory light.

FAG can be performed in many facilities using the FAG filter. Improvement of the clarity of FAG images, development of an auxiliary tool to position the FAG filter to a microscope adequately, and quantitative blood flow evaluation methods should be developed in the future; however, the FAG filter is currently a useful tool in neurosurgical surgery.

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Conflicts of Interest Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this article.

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Address reprint requests to: Tsuyoshi Ichikawa, MD, Department of Neurosurgery, Fukushima Red Cross Hospital, 11-31 Irie-cho, Fukushima 960-8530, Japan.
e-mail: ichikawa@fukushima-med-jrc.jp