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TECHNICAL NOTE - VASCULAR NEUROSURGERY - ANEURYSM

Universal fluorescence module for intraoperative fluorescein angiography—a technical report

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Abstract

Background Even in specialized centers, suboptimal aneurysm clipping can be as high as 12%. Intraoperative fluorescence angiography with indocyanine green and, more recently, fluorescein sodium have been shown to be a good method for intraoperative flow assessment. However, the cost with the apparatus it entails limits its widespread use. We have developed a low-cost universal fluorescence module (FM) designed to visualize fluorescein and perform intraoperative angiography. The purpose of this paper is to describe this device as well as to present our early experience with its use in the treatment of cerebral aneurysms.

Method A FM was designed and built using a cyan-blue narrow bandpass (460 to 490 nm) excitation filter and a yellow-orange longpass (blocking wavelengths under 520 nm) barrier filter mounted on a 3D-printed holding tray in a specific disposition to perfectly match the light source and the objective lens of the surgical microscope. It allowed switching from white light to fluorescence mode in a simple and sterile fashion. Its perfect attachment to the microscope was possible by reusing the lens fittings extracted from used original drape sets that would otherwise be discarded. Four patients underwent aneurysm clipping using the FM at two institutions from April to September 2018.

Results A bright green fluorescence against a dark background was observed after intravenous bolus of fluorescein. Blood vessels became obviously distinct from non-contrast-filled structures such as clipped aneurysms and the brain. Vascular anatomy could be appreciated without any distortion, including perforating arteries.

Conclusions Intraoperative fluorescence angiography was successfully performed with the use of this universal FM after intravenous injection of fluorescein sodium. This simple and low-cost device may be useful in resource-limited centers, where other sorts of intraoperative angiography are not available.

Keywords Fluorescein · Fluorescence module · Intraoperative angiography · Cerebral aneurysm

Abbreviations

DSA	Digital subtraction angiography
FM	Fluorescence module
ICG	Indocyanine green
3PHT	3D-printed holding tray
5-ALA	5-Aminolevulinic acid

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Introduction

The goal of aneurysm surgery is to completely occlude the sac without compromising the flow within parent and branching as well as related perforating arteries. Even in specialized vascular centers, postoperative angiographic studies show the risk of suboptimal aneurysm clipping by incomplete sac exclusion or inadvertent occlusion of related arteries, estimated to be 4–8% and 4–12%, respectively [4, 5, 12]. The gold standard to confirm adequate intraoperative clipping is digital

subtraction angiography (DSA). Importantly, it has been shown that intraoperative DSA led to modifications in aneurysm treatment in up to 12.4% of cases [17]. Nevertheless, its widespread routine use is hampered by the fact it is laborious, not free of complications (up to 2.6%), prolongs surgical time, and has an inherent cost [2, 7, 17]. In 2003, Raabe et al. described a new method for intraoperative assessment of vascular flow named near-infrared indocyanine green (ICG) video angiography. It consists of an intravenous injection of a fluorescent contrast (ICG) in combination with the use of microscope-integrated FM [13]. Since it is safe, relatively inexpensive, and practical and its accuracy is similar to intraoperative DSA (correspondence in 90% of cases), fluorescence angiography gained traction and gradually became a standard practice in many centers [14] .

More recently, fluorescein has also been successfully used to perform intraoperative angiography in substitution of or in conjunction with ICG [9, 15]. In fact, it may even be superior at high magnification in deep surgical fields [15]. Fluorescein also requires a FM to be well visualized, but unlike ICG, it does not require a special infrared camera to be detected. Currently, there are only two manufacturers whose microscopes support integrated fluorescein modules (YELLOW-560 by Carl Zeiss Meditec and FL560 by Leica Microsystems), both on their high-end models.

Many centers, especially in developing countries, do not have access to these costly high-end microscopes with integrated FMs. Some authors developed alternative low-cost fluorescein modules as an attempt to popularize fluorescence-guided surgery for both vascular and tumor surgery [6, 8, 11]. Based on these previous experiences and on the specifications of commercially available FMs, we developed a user-friendly low-cost device, capable of highlighting fluorescein and performing intraoperative fluorescence angiography.

The purpose of this paper is to describe a FM designed for fluorescein-guided surgery as well as to present our early experience with its use in the treatment of cerebral aneurysms.

Material and methods

Patients

The universal fluorescence system was used in 4 patients harboring aneurysms from April to September 2018 by the same surgical team at two institutions: Hospital Universitário Antonio Pedro and Hospital Municipal Miguel Couto. Patient's age and aneurysm characteristics are shown in Table 1.

Fluorescence module

We developed a 3D-printed tray, capable of holding optical filters in a specific disposition to perfectly match the light source and the objective lens of the surgical microscope, so as to serve as excitation and barrier filters, respectively (Fig. 1a). The excitation filter was a cyan-blue narrow bandpass (BN 470, Midwest Optics, USA), which has a useful range from 460 to 490 nm; the barrier filter was a yellow-orange longpass (LP515, Midwest Optics, USA), optimized to block wavelengths up to 520 nm.

The 3D-printed holding tray (3PHT) was designed to adapt to the lens fitting of an original microscope drape set, in substitution to its transparent glass (Fig. 1b). On its inferior surface, the 3PHT has a part designed to perfectly fit a second lens fitting (Fig. 1c).

We named FM the 3PHT coupled with a reused lens fitting extracted from original drape sets used in other cases that would otherwise be discarded (Fig. 1d).

The FM (3PHT + reused lens fitting) was kept inside the sterile drape while performing conventional surgery under white light (Fig. 2a). Practical switching to fluorescence mode is possible by uncoupling the lens fitting of the sterile drape from the microscope (Fig. 2b), followed by the FM attachment (Fig. 2c) and recoupling of the sterile drape onto the inferior surface of the fluorescence module (Fig. 2d). This could be done by the surgeons in a sterile manner as many times as necessary and without external assistance (Online Resource 1).

The cost with the FM was 575 dollars (including taxes), being 510 and 65 dollars for the set of optical filters and the 3PHT, respectively.

Fluorescein

After the placement of the universal FM, a bolus of fluorescein sodium 20% (5 mg/kg) is injected intravenously by the anesthesiologist, when intraoperative angiography is needed.

Surgical microscopes

This universal FM was successfully tested in the Zeiss OPMI VARIO S88, VARIO 700, and PENTERO 800. While on fluorescence mode, the light was turned up to its maximum in order to provide sufficient light to the surgical field.

Results

In all cases, a bright green fluorescence against a dark background was observed few seconds after the intravenous bolus of fluorescein (Fig. 3). Contrast-filled blood vessels became obviously distinct from non-contrast-filled structures such as

Table 1 Patient's age and aneurysm characteristics

	AGE (years)	Location	Aneurysm size	Status
Case 1	69	Left pericallousal artery	9 mm	Unruptured
Case 2	67	Right middle cerebral artery	7 mm	Unruptured
Case 3	64	Anterior communicating artery	7 mm	Unruptured
Case 4	29	Anterior communicating artery	5 mm	Ruptured

clipped aneurysms and the brain. Arterial and venous anatomy could be appreciated without any distortion. Even small vessels, such as perforating arteries, could be well visualized. Arterial and subsequently venous phases were clearly observed. Blood-brain barrier absent structures, such as the dura, become highly fluorescent in a few minutes. Blood vessels hidden by brain or blood clots were not seen until directly exposed to light. Small bleedings, as a result of arachnoid dissection, allowed contrast leakage and were also highlighted by the contrast. Upon removal of the FM, the normal color of the structures was preserved, even after the injection of fluorescein (Online Resources 2, 3, and 4). Due to fluorescein long clearance time, it was not possible to repeat the angiography.

Case 1: pericallousal artery aneurysm

A 69-year-old woman presented with a 9-mm left pericallousal artery aneurysm found on imaging done for memory deficit. She underwent elective surgery with a right fronto-parietal craniotomy followed by interhemispheric approach. After presumably adequate clipping, the FM was put in place; then, a bolus of fluorescein sodium was injected on a peripheral vein in the forearm. In 30 s, a bright green highlighted parent and branching arteries. The aneurysm remained dark and was considered excluded (Online Resource 2).

Case 2: middle cerebral artery aneurysm

A 67-year-old woman presented with an unruptured 7-mm right middle cerebral artery aneurysm found on imaging obtained for headache. She underwent elective surgery with a right pterional craniotomy followed by transsylvian approach. Superior and inferior trunks as well as a small artery attached to the aneurysm dome were found during aneurysm dissection. After clipping, the FM was put in place, then a bolus of fluorescein sodium was injected on a peripheral vein in the arm. In 15 s, a bright green highlighted the arteries and, a few

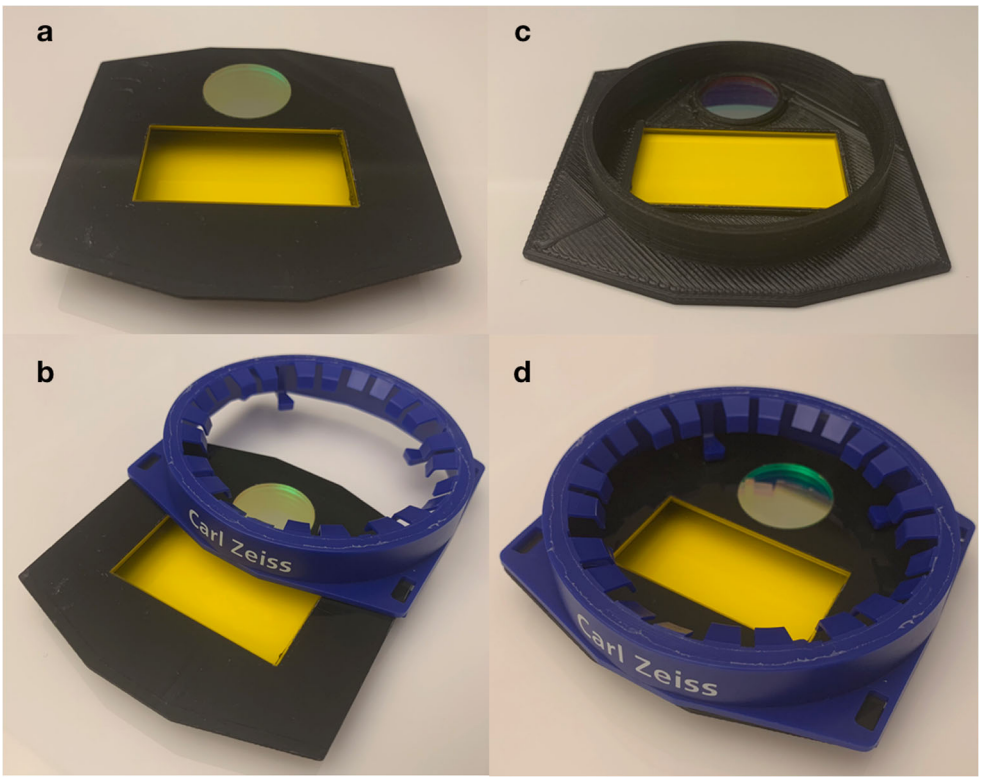

Figure 1 **a** 3PHT; **b** 3PHT being inserted in the lens fitting; **c** Part designed to fit a second lens fitting; **d** Fluorescence module

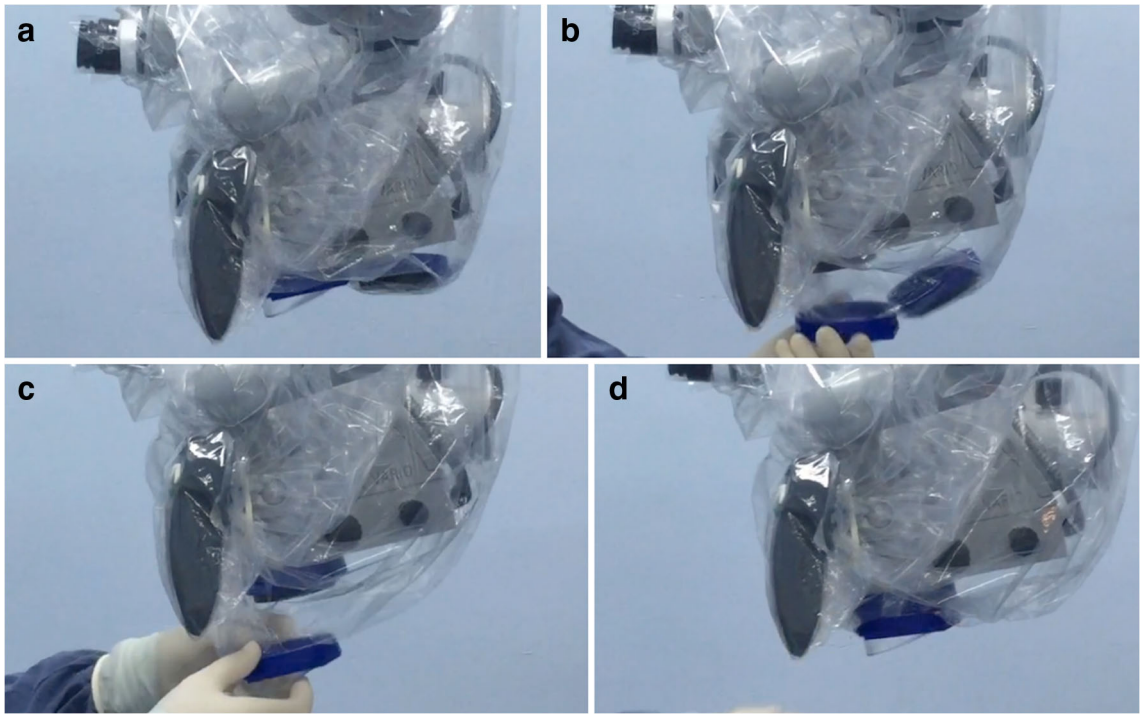

Figure 2 **a** Fluorescence module inside the sterile drape; **b** Uncoupling of the lens fitting; **c** Attachment of the fluorescence module; **d** Recoupling of the sterile drape

seconds later, the middle cerebral vein. The superior trunk could be easily seen; however, the inferior trunk could only be inspected after temporal lobe retraction and aspiration of a small clot. At this moment, a small artery, adherent to the aneurysm dome, was fluorescent as well and was considered patent (Online Resource 3).

Case 3: anterior communicating artery aneurysm

A 64-year-old man presented with an unruptured aneurysm seen on magnetic resonance imaging performed for seizure investigation. A 7-mm lobulated anterior communicating artery aneurysm directed superiorly was found. Patient underwent left pterional craniotomy (ipsilateral to the dominant A1) followed by transsylvian approach. A fenestrated clip was applied, with apparent preservation of parent and branching arteries. Fluorescein angiography was performed, which showed a very slow pulsatile filling of left recurrent artery of Heubner, consistent with stenosis. The clip was immediately repositioned. However, due to fluorescein long clearance time, a second confirmatory angiography, after clip revision, was deemed unfeasible. Postoperative imaging showed adequate clipping and no signs of ischemia (Online Resource 4).

Case 4: anterior cerebral artery aneurysm

A 29-year-old man was admitted after a thunderclap headache. Computed tomography showed subarachnoid hemorrhage (Fisher grade 3) and hydrocephalus. Patient became drowsy, disoriented, and without focal deficit (WFNS grade II). He underwent emergency external ventricular drainage, followed by cerebral angiogram. An anterior communicating artery aneurysm directed anteriorly was diagnosed. Surgery for aneurysm clipping was performed uneventfully the following day. Blood clots had to be judiciously removed to allow a good quality angiography. After clipping, fluorescein angiography was performed, confirming adequate clipping. Arteries hidden by clots did not become fluorescent until cleared.

Discussion

We describe a simple and practical low-cost device, capable of performing intraoperative fluorescence angiography with good anatomical precision and in real time. It was successfully tested in three different microscope models by Carl Zeiss Meditec. In theory, this system can be used in any microscope, by any manufacturer, with minor changes in the position of the optic filters. It allows switching from white light to fluorescence mode in a simple and sterile fashion. In addition, it is attached to the microscope with used original lens fitting approved by the manufacturer, hence minimizing the risk of damaging the microscope.

Numerous researchers have described devices capable of enhancing the visualization of fluorescein fluorescence in

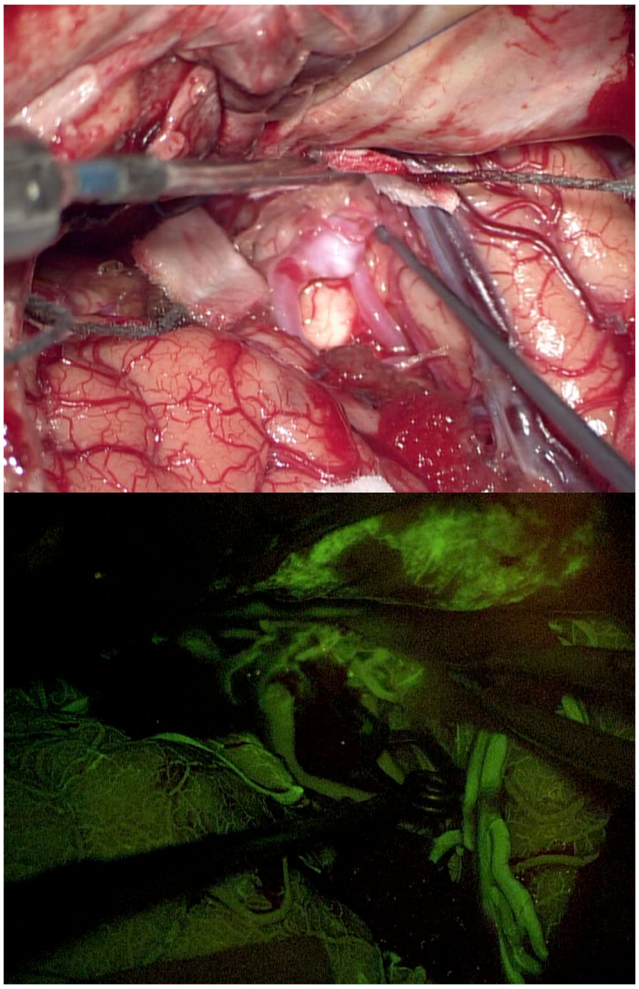

Figure 3 Before (upper) and after (lower) attachment of the FM followed by intravenous fluorescein bolus

neurosurgery for both vascular and tumor procedures. Microscope industry has also integrated fluorescein modules to their latest microscopes [15]. In brief, these modules consist in a set of optical filters that can be alternated with conventional white light at the touch of a button. This combination of filters allows lighting the surgical field with a cyan-blue light (wavelengths between 450 and 460 nm and 500 nm), optimal for fluorescence excitation (maximal at wavelengths between 465 nm and 490 nm), and detection of light at the spectrum above 510 nm (Leica Microsystems FL560 module whereas within 540 nm and 690 nm in YELLOW-560 module by Carl Zeiss Meditec), ideal to detect green-yellowish light emitted by fluorescein (480 to 680 nm range, maximal at 514 nm) [15].

Some authors report ingenious but complex systems that require the use of an excitation light source apart from the microscope using specially made probes or adapted endoscopes [1, 16, 18]. Others were relatively costly (up to US$ 4000–10,000) or had sterilization issues [6, 11, 16]. Some systems require the use of custom-made parts, which are difficult to be reproduced. For instance, Kiroiwa et al. reported a very convenient, yet complex, device that was able to electrically switch the fluorescence mode to white light using a remote control [8]. Lovato et al. designed and 3D-printed a very interesting device and reported its use for brain tumors [11]. Although this manufacturing technology is low cost, widely available, and can be easily reproduced, the complexity of designing the entire apparatus, especially the part that holds the device onto the microscope, should not be underestimated. Furthermore, the impact of the material used on the microscope integrity is unknown.

Fluorescein sodium is a contrast extensively used for decades mainly in the field of ophthalmology. It is inexpensive (around US$ 2), widely available, and safe, which makes it an attractive fluorescent dye for resource-limited centers. In ambulatory retinal angiography procedures, it has been reported that, by far, the most common side effects are nausea (2.24%) and vomiting (up to 7%) [10]. These symptoms are not experienced by patients during general anesthesia, as in most craniotomies. With respect to the related risk of severe reactions and death, intravenous administration of fluorescein seems to be extremely safe (1 in 1900 and 1 in 222,000, respectively) [19].

One aspect which makes fluorescein even more simple to use is that both of its excitation and emission lights are within the visible spectrum, hence it does not require special infrared cameras as in ICG angiography. The simple combination of optical filters is sufficient to fully explore its fluorescent properties in real time, allowing surgery to be performed under the fluorescence mode [15].

Even in centers where ICG video angiography is a standard practice in neurovascular surgery, fluorescein may play a role. ICG takes several minutes to be cleared from the blood stream, hence repeat angiography may lead to false positive [3, 9]. On the other hand, fluorescein long clearance time makes it impractical for repeat angiographies [9]. In this sense, the use of these two fluorescent dyes, along with their respective FMs, is an interesting alternative, allowing two angiographies to be performed sequentially, as in aneurysm cases which require clip repositioning [9].

This fluorescein FM may also be useful for flow assessment in other cerebrovascular surgeries, such as arteriovenous malformations and extracranial-intracranial bypasses, although we acknowledge further investigation is warranted.

Theoretically, this fluorescence system can be adapted for other fluorophores provided that both their excitation and emission lights are within the visible spectrum. Obviously, the set of optical filters must be properly changed. Porphyrin fluorescence, used to guide malignant glioma resection after the oral administration of 5-aminolevulinic acid (5-ALA), is a remarkable example.

Conclusions

Intraoperative fluorescence angiography was successfully performed with the use of this universal FM after an intravenous injection of fluorescein sodium. This simple and low-cost device may be useful in resource-limited centers, where other sorts of intraoperative angiography are not available.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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