Cureus

Open Access Review Article

DOI: 10.7759/cureus.199

Lighting Up Neurovascular Surgery

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Abstract

Patient care has been revolutionized by the introduction of fluorescent dyes and the incorporation of fluorescence technology in disciplines ranging from ophthalmology to neurovascular surgery. These technologies enable clinicians and surgeons to produce accurate and real-time images of difficult-to-see structures within the human body, providing a crucial step to not only understanding biological processes but also advancing treatments. Isosulfan blue, fluorescein, and 5-aminolevulinic acid have proven useful in multiple fields of medicine. Indocyanine green (ICG) is another key fluorescent dye. Combined with specialized intraoperative microscopes, it is ideal for vascular studies because it diffuses easily from vessels into the interstitial space. Ultimately, images of the vascular system within the surgical field can be observed on a video screen in real time. Today ICG allows neurosurgeons to evaluate the quality of an aneurysm clipping, the potential for residual flow in a fistula or malformation, and the patency of a bypass. With introduction of other dyes and improvements in imaging techniques, we are likely to see an expansion in application of fluorescent technology in neurosurgery and other fields, which will ultimately lead to better patient care and outcomes.

Categories: Neurosurgery
Keywords: fluorescence, indocyanine green, vascular neurosurgery, fluorescein

Received 08/28/2014
Review began 08/29/2014
Review ended 09/04/2014
Published 09/05/2014

Introduction And Background

The use of dyes has a rich history in medicine, dating back to the antiquities. The introduction of fluorescent dyes and the incorporation of appropriate filters for the use of fluorescence technology has revolutionized the care of patients in disciplines as wide ranging as ophthalmology and neurological surgery. Herein, we review the applications of fluorescence to vascular neurosurgery and highlight recent uses and upcoming applications in development.

Physics of fluorescence

Fluorescence is the emission of light by a substance that has absorbed electromagnetic radiation or other forms of light. In tissue, target molecules tagged with fluorescent probes can generate a high-contrast image of the tissue with the use of a confocal microscope. This tagging is especially useful because one fluorophore molecule can generate thousands of photons that are crucial to the sensitivity of microscopes. Additionally, a single fluorophore can be excited and detected repeatedly unless it is damaged due to quenching or photobleaching. Quenching is the loss of fluorescence to the surrounding molecular environment, and photobleaching is the irreversible destruction of a fluorophore due to the generation of reactive oxygen.

Using a confocal microscope, fluorophores are excited with a laser beam that emits the corresponding excitation wavelength. Before excitation, the fluorophore is in the molecular ground state, but after a photon of light is absorbed by the molecule, electrons move to a higher energy excited state. Fluorescent light is produced when excited electrons lose energy to the environment and return to the lowest excited singlet state; the electrons then move back to the ground state and simultaneously emit fluorescent light at a longer wavelength than the excitation light.

Every type of fluorophore has an extinction coefficient, which indicates its efficiency in absorbing excitation light at a specific wavelength. A larger extinction coefficient indicates a greater chance for light absorption, and the coefficient is proportional to the fluorescence output of each fluorophore. The number of fluorescent photons that a fluorophore emits per excitation photon absorbed is called the quantum yield. Because of their unique configurations, fluorophores also have different excitation and emission spectrums. The emission spectrum of a fluorophore provides the wavelength of maximum absorption, and the excitation spectrum provides the wavelength of maximum fluorescence emission. In a pair of excitation and emission spectrums, there can be an overlap between the higher excitation wavelengths and lower emission wavelengths. The difference is called Stokes shift, and it is caused by the loss of excitation energy during the electrons' return to the ground state. This overlap can cause the brighter excitation light to overwhelm the emission fluorescence under a microscope; however, the overlap can be eliminated with the proper excitation filter, emission filter, and dichromatic beamsplitter. In the research setting, confocal fluorescence microscopy produces images through a process of stimulated emission depletion (STED). Invented by Stefan

W. Hell in 1994, STED provides resolution by selectively deactivating fluorophores to enhance an area.

Fluorescent dyes used in medicine and surgery

The ability to produce images of what is difficult to see within the human body is a crucial step in the understanding of biological processes. Before the advent of fluorescent dyes, a variety of non-fluorescent dyes was used in medical applications. The classic application of dyes in medicine was the gram stain used to identify different types of bacterial species. After the advent of fluorescent technology, a huge number of dyes with fluorescent capabilities improved the quality of images that could be clinically used.

Isosulfan blue is a dye used to visualize the lymphatic system, and it has been useful in localizing sentinel lymph nodes in breast cancer patients. Cancerous tissue can be removed through isosulfan blue-guided surgery, but its use has been associated with a significant number of allergic reactions [1-2]. Indigo carmine is commonly used as a pH indicator, but it is clinically used as a dye to detect amniotic fluid leaks. During surgery, intravenous indigo carmine highlights the urinary tract as it is filtered from the blood and colors the urine blue. In some cases, it can cause a potentially dangerous increase in blood pressure, but it allows the structures of the urinary system to be visible and observed for any leaks [3].

One of the very first fluorescent dyes to be developed was fluorescein. In 1871, Adolph Von Baeyer synthesized Spiro[isobenzofuran-1(3H),9'-[9H]xanthen]-3-one, 3',6'-dihydroxy and he received the Nobel Prize in chemistry. One of the earliest medicinal uses of fluorescein was in 1882, when Paul Erlich used uranin, the sodium salt of fluorescein, to observe the secretions of the aqueous humor in the eye. Now, fluorescein has many different applications in medicine and is commonly used to label and track cells. Today, the sodium salt of fluorescein is used to diagnose corneal abrasions, corneal ulcers, and herpetic corneal infections. Intravenous or oral fluorescein is now used in brain surgery, but was initially used in fluorescein angiography to diagnose macular degeneration, diabetic retinopathy, intraocular tumors, and intraocular inflammation.

5-aminolevulinic acid (5-ALA) was initially used in photodynamic therapy for the clinical treatment of cancer patients. In photodynamic therapy, 5-ALA is administered and then activated by light. At the time, the new treatment was superior to the others because it was non-invasive, produced good cosmetic results, was tolerable to patients, was able to treat multiple lesions quickly, could be used for patients who refused surgery or had pacemakers, could be applied in more specific locations, and could be applied repeatedly [4]. In 2000, researchers began to think about the potential of 5-ALA for fluorescence-guided tumor resection. The successful and complete removal of tumors is crucial to patient survival, so a more accurate indication of unhealthy tissue was needed. 5-ALA is important because it induces the accumulation of fluorescent porphyrins in glioblastomas, and all fluorescing tissue can be identified and removed from the patient [5].

Indocyanine green: Applications in medicine

Indocyanine green (ICG) is commonly used for vascular studies, and is one of few dyes used in humans. It is ideal for vascular studies because it diffuses easily from vessels into the interstitial space. After being granted FDA approval in 1959, ICG was initially used in hepatic function diagnostics and later in cardiology [6]. It became possible to determine renal blood flow using ICG, and eventually it was used to research and diagnose processes in the choroid of the eye [7]. Since 1980, imaging technology has improved vastly and many technical difficulties have been removed. In more recent times, ICG has been used in fluorescent angiography, ophthalmology, determining cardiac output, testing hepatic function, determining liver blood flow, navigation for sentinel lymph node biopsy with tumors, diagnosis of rheumatic diseases, vascular neurosurgery, detecting lesions in the breast, and tracing perfusion.

Today, the use of ICG for angiograms of the eye is fairly common, and is replacing fluorescein angiography because it has better photon penetration capabilities. ICG can be used to visualize the blood vessels within the eye and to diagnose various visual disorders. In breast adenocarcinoma, ICG is taken up by mammary tumors and can be used to detect lesions [8]. Multiple groups have also shown that ICG can be used to identify vascular abnormalities within the gastrointestinal tract and indicate the severity of burns [9].

Review

Indocyanine green in neurosurgery

In neurosurgery, fluorescein was first used to visualize cerebral blood flow, but it became clear that ICG was more advantageous for clinical use. The light emission of ICG is superior to fluorescein and more easily detectable, with few negative reactions from patients. Some of the earliest applications of ICG were in 1985 during investigations of factors that affect ICG clearance [10]. Blood flow can now be tracked in vessels less than 1 mm in diameter without complications [12]. In rat and human models, it has also been proven that ICG angiography can improve tumor localization and enable the assessment of post-resection margins with increased sensitivity [9]. Because of its accuracy, ICG angiography can provide information regarding the patency and malformation of vessels in real time.

Clinically, ICG is administered to the patient intravenously at a recommended dose of 0.2–0.5 mg/kg. Once it has been injected, ICG is bound by globulins and remains within blood vessels until it is excreted through the liver. Ultimately, images of the vascular system within the surgical field can be observed on a video screen in real time. First, the field is illuminated by a near infrared light source with the proper wavelength for the ICG absorption spectrum. The ambient and excitation light should be blocked by an optical filter so that only the fluorescent light is visible. After the dye has been administered, the fluorescence is activated and then recorded by a video camera. ICG angiography is an integrated technique that requires the use of a specialized surgical microscope (Carl Zeiss Ltd., Cambridge, MA) that integrates near-infrared imaging into the surgical microscope to provide high-resolution and high-contrast images.

Applications in Aneurysm Surgery

In an early study in 1985 by Chauvin, et al., 14 patients underwent aneurysm surgery using ICG; their changes in hepatic plasma flow during sodium nitroprusside-induced hypotension were studied. There was no correlation between blood pressure and ICG clearance, and it was demonstrated that ICG clearance is only affected by hepatic plasma flow regardless of hypotension [10].

Sato, et al. used ICG to measure the circulating blood volume in 34 patients with subarachnoid hemorrhages and 20 patients with neurosurgical disorders as a control group. The mean blood volume of patients with subarachnoid hemorrhages was lower than the control patients; the blood volume in females with hemorrhage was decreased more significantly than the males [13]. This showed that actively measuring blood volume during aneurysm surgery using ICG might be necessary to preserve the normal volume when temporary vascular occlusion is required.

In 2002, a new method for monitoring cerebral oxygenation and hemodynamics in patients with subarachnoid hemorrhages was developed. To measure cerebral oxygenation and perfusion in patients, Keller and colleagues used a technique combining near infrared spectroscopy and ICG dilution. They analyzed the cases based on the decomposition in pulsatile and non-pulsatile components of the absorption data before and during the flow of ICG through the blood vessels under the near infrared spectroscopy-detector [14]. This method was an easier and more efficient way than standard techniques to detect and treat radiographic cerebral vasospasm after subarachnoid hemorrhage.

In 2003, Raabe, et al. showed that ICG can be used for the intraoperative assessment of vascular flow within the brain. This was the first in vivo demonstration of blood flow in cerebral vessels documented with ICG. In 12 aneurysm cases, ICG was used intraoperatively without any side-effects; the time course of ICG angiography was divided into arterial, capillary, and venous phases. In three cases, the information provided by the live images significantly changed the surgical procedure [15].

In a study by Raabe and colleagues of 20 patients with intracranial aneurysms, ICG permitted the real-time assessment of vessel patency and aneurysm occlusion; ICG allowed the surgeon to see perforating arteries with a diameter of less than 1 mm. In two cases, clip correction was required, and the intraoperative findings correlated with the postoperative digital subtraction angiography [16]. The study showed that the use of ICG could improve surgical procedures and reduce the need for intra- or postoperative angiography.

Applications in Cerebral Arteriovenous Malformations

ICG has been used widely in treating spinal and cerebral AVMs.

Takagi, et al. reported on a child with a cerebral AVM, where ICG videoangiography showed residual nidus of diffuse-type AVM. It was shown that the use of ICG is a safe and simple way to assess the circulation within the brain. This demonstrated that ICG videoangiography could be helpful in the resection of residual cerebral AVMs, and especially in cases of diffuse-type AVMs [17].

In 2009, Killory and colleagues investigated the application of intraoperative ICG in 10 consecutive AVM surgeries. The use of ICG angiography was useful to the surgeon in nine cases, and in eight patients, it helped to distinguish AVM vessels. In three of the four patients undergoing a post-resection injection, the ICG indicated that there was no residual arteriovenous shunting. In one patient, it helped to identify a small AVM nidus that was otherwise not apparent within a hematoma. They discovered through digital subtraction angiography that there was residual AVM in two of the 10 patients, which required further resection [18]. This study showed that ICG angiography can distinguish AVM vessels from normal vessels, but is less helpful with deep-seated lesions or when AVM vessels are not on the surface. It also suggested that ICG angiography can be used in addition to digital subtraction angiography, but cannot replace it.

ICG has also been used for assessment of arteriovenous micro-malformation (micro-AVM) of the trigeminal root diagnosed during microvascular decompression for trigeminal neuralgia. Ferroli, et al. discovered that the enlarged petrosal vein was arterialized, and that the trigeminal root was embedded in a tangle of abnormal arterialized vessels. The surgical team was able to recognize the micro-AVM because the ICG showed that the flow in the arterialized petrosal vein was anterograde [19]. This showed that ICG

videoangiography is suited for determining the flow dynamics of blood vessels.

Hänggi and colleagues studied 15 patients undergoing surgical resection of intracranial AVMs; intraoperative ICG videoangiography was used to analyze the malformations. In two cases, the ICG videoangiography provided information that changed the surgical strategy. In all but one case, the postoperative angiogram corresponded to the last ICG examination performed after the resection, and there were no side-effects related to ICG injection [20]. This showed that the use of ICG was safe and that it reveals information that can change a surgical plan.

In a study of three cases of cerebral arteriovenous malformations, the feeding arteries, the draining veins, and nidus in all patients were easily identified using ICG [21]. This demonstrated that with the help of color map and intensity diagram function, the feeders, drainers, and nidus of a cerebral AVM can be identified easily through ICG videoangiography. In a similar study, Faber, et al. combined ICG videoangiography and FLOW 800 software to assess the time-dependent intraoperative blood flow during surgical removal of cerebral AVMs. In two patients, this technology gave color-encoded visualization of blood flow distribution with high temporal and spatial resolution [22]. The cases demonstrated that real-time analysis of vessel architecture increases the efficacy and safety of AVM removal.

Zaidi and colleagues studied 130 patients undergoing surgical resection of cerebral AVMs; 56 patients had ICG videoangiography used at some point during the operation, and the other 74 did not. ICG videoangiography was more often used in AVMs that were lobar and located near the cortical surface; it was less useful when the AVMs were located in the posterior fossa. The results showed that ICG videoangiography did not affect clinical outcomes or reduce the incidence of residual disease, but was helpful during some operations. The surgeons concluded that it should be used to make a surgical plan for superficially located AVMs, but it cannot be an isolated imaging modality to confirm residual disease [23].

Recently, Fukuda, et al. observed the flow dynamics during surgery for AVMs in seven patients with FLOW 800 using ICG videoangiography. They recorded changes in flow dynamics in the superficial AVM components, the adjacent cortical artery, and the cortical vein surrounding the AVMs [24]. The experiment showed that at various stages of resection, FLOW 800 analysis with ICG videoangiography could indicate the hemodynamic status of the AVMs and surrounding brain.

Applications in Spinal Vascular Malformations

ICG videoangiography has also been used intraoperatively to treat spinal vascular malformations. ICG videoangiography gave direction to the vascular anatomy as demonstrated by the preoperative angiogram.

Walsh, et al. showed in one case that the ICG videoangiography led to the complete obliteration of a large AVM, but in another case, a diffuse intramedullary component could not be identified. In the second case, a spinal angiogram revealed a significant residual diffuse nidus within the cervical cord and thus revealed a limitation of ICG videoangiography [25]. Despite this, ICG provided useful information about arteriovenous flow and helped to ensure the complete removal of a spinal AVM.

Hettige and Walsh reported on one patient with a spinal dural arteriovenous fistula in whom ICG was injected intravenously. Dynamic filling of the abnormal vasculature was observed. A clip was applied to the fistulous connection, and ICG video angiography showed the interruption of the fistula and the preservation of the associated spinal artery [26]. The experiment demonstrated that ICG could shorten surgical time and provide reassurance of completeness. In a similar case, a patient underwent T7-9 bilateral laminectomies for microsurgical clip occlusion. ICG was used twice: before clip placement to identify the arterialized veins of the fistula, and after clip placement to confirm obliteration of the fistulous connection and restoration of normal blood flow [27]. ICG videoangiography is helpful because it can be used to map the anatomy in real time during surgery and confirm that the fistula has been obliterated.

Hanel and collaborators studied six patients undergoing surgery for spinal dural arteriovenous fistulae. ICG videoangiography identified the fistulous point(s), feeding arteries, and draining veins in all cases [28]. ICG videoangiography can serve as an independent form of angiography or as a complement to intra- or postoperative digital subtraction angiography.

Raabe, et al. analyzed the use of ICG videoangiography during surgeries for two patients, one with a spinal dural fistula, and one with an intracranial fistula. The image quality and resolution were excellent, and allowed intraoperative real-time assessment of the cerebral or spinal circulation [15].

In Schuette, et al.'s study of 25 patients, 13 with intracranial fistulae and 12 with spinal fistulae, ICG videoangiography was used during surgery. ICG allowed visualization of the fistula with precision, there were no complications, and the imaging confirmed fistula obliteration [29]. In another study that included one patient suffering from an intracranial fistula, ICG videoangiography was also helpful during the course of surgery [30].

Applications in Cerebral Artery Bypass Surgery

To increase cerebral blood flow, patients may need an extracranial-to-intracranial (EC-IC) bypass. The procedure is a potential treatment for ischemic stroke, but is only used in a very select group of patients.

Woitzik, et al. evaluated whether ICG videoangiography is suitable for intraoperative confirmation of EC-IC bypass patency. In their study, 11 patients had hemodynamic cerebral ischemia, 18 had Moyamoya disease, and 11 had complex intracranial aneurysms. ICG was injected systemically via an intravenous bolus injection in all of the patients. Superficial temporal artery-middle cerebral artery (STA-MCA) bypass surgery was performed 35 times in 30 patients (five patients with Moyamoya underwent bilateral procedures), superficial temporal artery-posterior cerebral artery bypass surgery was performed in two patients, and saphenous vein (SV) high-flow bypass surgery in eight patients. ICG videoangiography was used to identify four non-functioning STA-MCA bypasses, and in two cases of SV high-flow bypasses, it revealed stenosis at the proximal anastomotic site. All of the ICG videoangiography findings could be validated postoperatively through digital subtraction or computed tomography angiography [31]. Because it provided visualization of cerebral arteries, the bypass graft, and brain perfusion, the authors concluded that the use of ICG might reduce the incidence of early bypass graft failure.

In a study published by Peña-Tapia, et al., 30 patients with hemodynamic cerebrovascular insufficiency due to steno-occlusive arterial disease underwent EC-IC bypass surgery. ICG angiography was used intraoperatively to determine the number, diameter, and length of the exposed cortical arteries [32].

Esposito and colleagues tested the feasibility of ICG videoangiography for identifying cortical recipient vessels to perform selective-targeted EC-IC bypass surgery in seven consecutive patients treated for complex middle cerebral artery aneurysms. In all of the cases, the technique enabled reliable identification of the cortical recipient artery and eliminated the risk of erroneous revascularization of non-involved territories [33].

In another trial, ICG was used to evaluate bypass blood flow in 13 Moyamoya disease and 21 non-Moyamoya ischemic stroke patients during STA-MCA anastomosis. The ICG perfusion area in Moyamoya patients was significantly larger than that in non-Moyamoya patients, and the cortical oxygen saturation in the Moyamoya patients was significantly lower than that in the other patients. The study showed that ICG angiography with injection of ICG into the bypass artery could allow quantitative assessment of bypass blood flow [34].

ICG videoangiography was also used by Horie, et al. to assess postoperative cerebral hyperperfusion in a prospective study of 47 patients who underwent STA-MCA single bypass surgery. In this investigation, 36 patients had Moyamoya disease (22 adult cases and 14 pediatric cases) and 11 patients had atherosclerosis. Adult Moyamoya disease with postoperative cerebral hyperperfusion was associated with a longer ICG peak time, but there was no correlation between the ICG peak time and preoperative cerebral blood flow or vascular reserve [35]. The study demonstrated that ICG videoangiography provides different characteristics of bypass flow among adult and pediatric Moyamoya disease patients and those with atherosclerosis. Uchino and colleagues performed a similar study of 10 patients. ICG was evaluated for its capability to predict of postoperative hyperperfusion during surgery for Moyamoya. The experiment also confirmed that ICG videoangiography is useful in evaluating changes in cortical perfusion after bypass procedures for Moyamoya and can predict early-onset hyperperfusion in Moyamoya patients after direct bypass [36].

In another study, Januszewski, et al. analyzed the use of ICG videoangiography in 33 bypass patients because intraoperative graft patency had not always correlated with graft flow previously. In all of their cases, the type of flow observed through the graft was confirmed on postoperative imaging findings, and it was determined that ICG videoangiography is reliable to evaluate flow in cases of EC-IC or intracranial-intracranial (IC-IC) bypass for ischemic stroke [37].

Conclusions

Fluorescent technology has revolutionized the practice of medicine in general and neurosurgery in particular. Today, ICG allows surgeons to evaluate quality of aneurysm clipping, the potential for residual flow in a fistula or malformation, and the patency of a bypass. With introduction of other dyes and improvements in imaging techniques, we are likely to see an expansion in application of fluorescent technology in neurosurgery.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might

have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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