Low-Cost Fluorescein Detection System for High-Grade Glioma Surgery

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■ BACKGROUND: **Intraoperative fluorescein detection has been used in the fields of vascular and oncologic neurosurgery since 1948. Modifications of the optics in order to enhance the fluorescence contrast under microscopic view have been developed by many authors. The industries, during the past 10 years, provided commercial high-cost optimized apparatuses. Reviewing the literature, we found that the prototypical techniques were definitely inexpensive but lacked reliability, reproducibility, and standard legal norms.**

■ METHODS: **We describe the developing of a fluorescein detection system that could be economic, simple, effective, and law abiding.**

■ RESULTS: **We employed a commercial violet-blue filter designed for fluorescein excitation in endoscopic procedures and used commercial photographic yellow optical filters for fluorescence detection. All the instrumentation is cleared for clinical use, and its cost is up to 200 times lower than commercial apparatuses.**

■ CONCLUSION: **Our results show a good distinction of fluorescein-stained structures, with overall acceptable operating light conditions.**

INTRODUCTION

Intraoperative fluorescein detection has been used in neurosurgery for multiple purposes: Since the pioneering work by Moore in 1948, many papers have been investigating its use mainly in the fields of vascular and oncologic surgery.[1] Thanks to its extensive use in the ophthalmology field, fluorescein showed a favorable safety profile at low doses (<10 mg/kg),[2] but there have been some reports of major adverse reactions as the dose increases.[3,4] Even if it has been recently employed at high doses without filters,[5-7] many authors tried some modification of the optics in order to enhance the fluorescence under microscopic view at low doses, too. The first surgeons who pioneered the use of filter systems were Feindel and colleagues in 1967. The first modification in the optics of a microscope was carried out in 1994 by Wrobel et al., who applied a filter system tailored on the fluorescence spectrum of fluorescein.[8,9] In particular, they constructed an apparatus consisting of a cyan-violet light source shedding light to the surgical field via a fiberoptic system and a yellow filter placed on the microscope oculars or on plastic goggles worn by the surgeon. Both color modifications were performed with the aid of photographic gelatin filters. Although they concluded that there was a general usefulness in this system, they complained that "… the incident illumination provided by the fiberoptic system is not sufficient to permit safe manipulation…" and that operations were generally carried out in "low-light conditions." These limitations were partially overcome in two 1998 publications: Kuroiwa et al. and Stummer et al. reported the use of glass interference filters tailored on the fluorescence spectrum of fluorescein and porphyrins, respectively.[10,11] Similarly, in 2003 new research was published on the use of indocyanine green fluorescence (ICG) in neurosurgery.[12] The development of these fluorescence systems was empowered by industries—the first articles in the field of neurosurgery describing the use of commercial microscopes equipped with fluorescence modules date back to 2005 for ICG, 2006 for 5-ALA, and 2013 for fluorescein.[13-15] The aim of this study is to outline the development of a low-cost equipment for fluorescein detection in neurosurgery, addressing regulatory and safety issues and comparing its cost-benefit profile with other commercial apparatuses.

MATERIALS AND METHODS

We employed a light filter originally designed for endoscopic procedures aiming at the detection of skull base

Key words
- Endoscopy
- Filter
- Fluorescein
- Glioma
- Low-cost

Abbreviations and Acronyms
5-ALA: 5-*aminolevulinic acid*
ICG: Indocyanine green

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Citation: World Neurosurg. (2016) 88:54-58.
http://dx.doi.org/10.1016/j.wneu.2016.01.017

*Journal homepage: **www.WORLDNEUROSURGERY.org***

*Available online: **www.sciencedirect.com***

cerebrospinal fluid (CSF) fistulas (Karl Storz GmbH & Co, Tuttlingen, Germany). This device has a built-in thermal radiator for heat dispersion and a set of 3 glass interference filters: neutral, blue (centered on 490 nm), and violet-blue (centered on 465 nm). The filter was connected to both a 300-watt Xenon light source and a fiberoptic light cable. The distal end of the light cable was held by hand near the surgical field or fixed with Velcro disposable strips to a brain retractor in order to obtain a stable, nonhindering placement of the light source (Figure 1). Before human testing, we verified that no significant heating took place after a prolonged, filtered illumination at close range of the surfaces enlightened. In particular, no increase in temperature as recorded by a surface thermometer was noted after a 1-hour-long exposure to the filter light at a 3-cm distance. This is mainly due to the violet-blue filtering that excludes most infrared emissions. Both the built-in light of the microscope and the surrounding lights of the operating room were dimmed so as not to interfere with the light modifications. In order to optimize visualization, we also employed yellow high-pass filters. For microscopic view we employed commercial photographic filters customized to fit on top of the microscope oculars (XSOURCE), whereas for macroscopic view we employed commercial ultraviolet yellow glasses (ORAO) (Figure 2). All filters could be easily switched off or removed from the light paths during the operations.

As for legal issues, in accordance with the Clinical Engineering Service of our hospital, no structural modification was made on the microscope or to the endoscopic instrumentation. We are currently enrolling patients in a registered clinical trial with this apparatus ("GLOWOMA: Glioma Lesions Outlining With Optics Modification Assistance: a phase II trial evaluating fluorescein-aided glioblastoma surgery"—EudraCT Number: 2015-003402-16). To all patients who have given their informed consent, 5 mg/kg of sodium fluorescein at 20% (Monico S.p.a., Mestre, Italy) are administered intravenously at anesthesia induction.

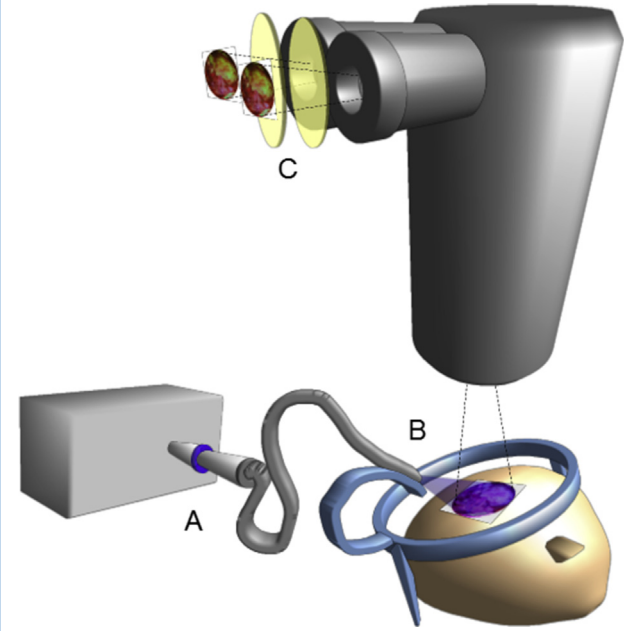

Figure 1. Filtering system setup. Three-dimensional rendering of the filtering system employed. (**A**) Xenon light source with violet-blue filter for endoscopic procedures. (**B**) The distal end of the endoscopic light cable is fixed to a retracting blade. (**C**) Yellow photographic filters are superimposed to the microscope oculars.

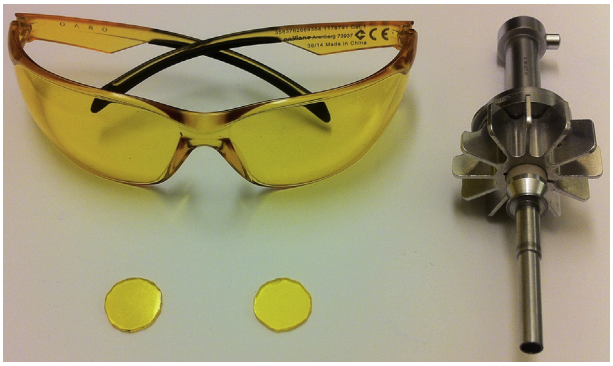

Figure 2. Filtering hardware. Commercially available yellow glasses. Yellow photographic filters custom-shaped to fit the microscope oculars. Endoscopic light source blue-violet filter.

RESULTS

In our initial experience based on 4 glioblastoma patients, we were able to detect fluorescence in all of the cases. The dura was already vividly green from the beginning, and we didn't notice any dye attenuation throughout the intervention. Our impression, confirmed by the use of neuronavigation, is that the fluorescent staining occurs in the same areas that are enhanced by gadolinium in the magnetic resonance imaging scans, while necrotic areas do not retain the dye except for some degree of greenish staining of the intracystic fluids and necrotic melted tissues. In our opinion, this has 2 major advantages: firstly, the nodules enhancing a vivid contrast are in this way easier to be identified, thus somewhat speeding up the resection procedures. Secondly, by our experience, the fluorescein staining allows us to better identify the contrast-enhancing boundaries of glioblastomas in the last phases of the intervention (Figure 3). To date, gross total removal was achieved in all of the patients and no drug-related side effects were noted (Figure 4).

DISCUSSION

The evolution of fluorescence detection systems has been revolutionized by the industries. The diffusion of these devices is increasing, but the image quality has notably increased, too. Although the industries are to be commended for their efforts, these systems still need a cutting-edge microscope and accessory modules for all the different fluorescent dyes, implying that the encompassing total cost of the instrumentation technology easily exceeds few hundred thousand euros. In reviewing literature we found that the prototypical apparatuses were