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LED light source for fluorescence endoscopy using quantum dots

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Abstract

We present an LED light source for use with standard clinical endoscopes to enable visualization of tissues labeled with quantum dots (QDs). QD-assisted endoscopy may improve the outcome of surgical endoscopic procedures by identifying specific tissue types. QDs offer several advantages over current fluorescent stains due to their high target selectivity, long-lasting fluorescence, large excitation and narrow emission bands, and multiplexing capabilities. The prototype presented is compact, modular in design, and was built at low cost making it competitive with commercially available light sources. The device's efficiency is evaluated by measuring light intensity at discreet locations and by successfully illuminating a chicken tissue sample non-specifically labeled with a 250nM or 500nM QD solution. Ultimately, this device serves as a step towards incorporating QDs into real time, image-guided surgical procedures.

SECTION I

INTRODUCTION

ENDOSCOPY is a medical procedure used to evaluate the interior surface of organs by inserting a tube (rigid or flexible) carrying a camera into the body. This provides real-time visual information about physiological conditions, such as the presence of cancer, where discriminating accurately between normal and diseased areas is crucial. However, the margins of malignant regions may not be readily detectable when the tissue is viewed with standard white light illumination. Thus, fluorescence-based techniques have been applied

during endoscopy to assist in discriminating between normal and diseased tissues [1] [2] [3] [4] [5] [6] [7] [8].

Both autofluorescence and artificially introduced fluorophores are of clinical interest. Biological tissues autofluoresce when excited by UV or visible light due to *in vivo* fluorophores such as connective tissues, coenzymes, aromatic amino acids, and porphyrins [9]. Several commercial autofluorescence detection devices have been developed for use during endoscopic procedures, including LIFE (Novadaq), D-Light (Karl Storz) and SAFE 1000 (Pentax) [10] [11] [12] [13]. These devices typically consist of a light source, cameras, and filters capable of switching between white and excitation light. However, these systems have notable limitations. Autofluorescence is the collective result of the activity of many *in vivo* fluorophores, and as such, it does not strictly discriminate among tissue types: the autofluorescence spectra of healthy and diseased tissue can significantly overlap [14]. Other limitations include high false-positive readings, subjective results, and cost [15], [16].

Fluorophores may also be artificially introduced into tissue. Many of these fluorophores excite in the near-infrared region, requiring dedicated cameras and computers to overlay images for the surgeon. Several near-infrared imaging systems are in development, such as the FLARE/mini-FLARE [17]. However, these systems are also subject to limitations. For example, dyes such as the clinically approved indocyanine green (ICG) have low thermal stability, undergo rapid photo bleaching, and bind to plasma proteins, resulting in quick elimination from the body [18], [19].

Quantum dots (QDs) have the potential to be a valuable addition to the current repertoire of fluorescence-based techniques in endoscopy. QDs are fluorescent nanoparticles that can be conjugated with antibodies and delivered to specific molecular and cellular targets [20], [21]. Specific advantageous properties of QDs include: (i) high target specificity, (ii) broad excitation and narrow emission ranges, (iii) long-lasting fluorescence (e.g. resistance to photo bleaching) and (iv) multiplexing capabilities. QDs are still in the phase of research and development and are not currently approved for clinical use. However, a recent study investigating the effects of QDs *in vivo* in primates has indicated that toxicity effects may be sufficiently low that the application of QDs in image-guided surgery could be considered [22]. The ‘stepwise’ incorporation of QDs into endoscopic procedures may therefore be useful. The device presented in this paper represents a movement towards this goal as it may be attached to a standard clinical endoscope to enable viewing of QD-labeled tissue.

SECTION II

METHODS

A. Quantum Dots—The prototype is tested with QDs excited by wavelengths at 450nm and emitting at 620nm (visible red light). However, it may accommodate any QDs of interest by swapping LED modules or by adding filters for specific excitation or emission wavelengths.

B. Design of Light Source—The LED light source was designed to selectively excite quantum dots and to provide additional white light for surgical guidance. The functional

parameters considered when designing the light source were (i) white light illumination comparable to commercially available xenon light sources, (ii) light emission at QD-specific wavelengths, (iii) independent on/off and intensity controls for each type of light, (iv) compatibility with different fiber optic cables, (v) efficient light capture, (vi) low power consumption, and (vii) compact size/portability.

The optical components of the light source should allow for the efficient coupling of light from the LEDs and into the fiber optic cable (Figure 1). It is desirable to focus light directly at the cable entrance at a minimal distance from the light source to minimize loss due to scattering. A small angle of convergence is also desirable to match the numerical aperture (NA) of commercial fiber optic cables, which is generally inversely proportional to length.

A custom 7 LED assembly (Luxeon Star, SR-02-CUSTOM) was mounted to a 4.1 °C/W round heat sink with thermal tape for heat dissipation. A 12 VDC fan was placed directly behind the heat sink to improve airflow. The LED assembly consists of 4 royal blue (447.5 nm, 910 mW ea.) and 3 neutral white LEDs (4100K, 230 1m ea.). The royal blue LEDs match closely to the 450 nm excitation wavelength of the selected QDs. The neutral white LEDs are intended to match typical white light sources used in endoscopic procedures for cavity illumination. It should be noted that other LED combinations could easily be employed to match the excitation wavelengths of other QDs or fluorophores. Light emitted from the LED assembly is captured by a 7-cell concentrator lens (Polymer Optics, #263) capable of generating a small beam waist with 85% efficiency at a working distance of 25mm. A double concave lens further manipulates the light by increasing the focal length of the system and collimating the beam for increased optical efficiency (−25.0 mm focal length; Edmund Optics, NT32–992). Next, the light passes through an aspheric condensing lens (16.3 mm back focal length; Edmund Optics, NT43–988), which minimizes spherical aberrations and focuses the previously collimated light directly at the fiber optic cable entrance at a theoretical convergence angle of 23°, making it compatible with most 0.20 NA cables. This study utilizes a donated 9-foot light guide with a bundle diameter of 3.0 mm.

A key goal in designing the circuitry of the light source was to maintain flexibility in terms of components, power sources, and number of LEDs. A sample circuit diagram is shown in Figure 2. The system is comprised of independent circuits for the royal blue and neutral white LEDs, each connected in series to maintain equal current. A 700 mA BuckPuck DC driver was employed to maintain the current regardless of input voltages or the number of LEDs. A potentiometer allows manual control of the brightness, which may be useful if the device is used in combination with other light sources. Finally, each circuit features a switch permitting independent on/off controls for the royal blue LEDs, neutral white LEDs, and fan. Presently, each LED circuit is powered by two 9V batteries, theoretically providing 1.5 hours of battery life at full intensity (500–600mAh ea.), making the system portable and capable of operating away from a traditional operating room and power sources.

Another key advantage of the light source is that its base is primarily produced through rapid prototyping techniques. In this iteration, separate component bases were printed with a 3D plastic printer (PP3DP, UP!3d), permitting quick and easy interchanging to meet situational needs or make modifications. Each component base mounts quickly to a T-slotted beam

(80/20 Inc., 25–2514) with a nut and washer. This allows the operator to calibrate the system in one dimension, adjusting the angle at which light enters the fiber optic cable. The entire system is placed inside a project box with two case fans for improved airflow (Figure 3).

C. Component Testing—The device was evaluated by measuring the light intensity ($\mu\text{W}/\text{cm}^2$) at different positions with a meter (Newport 1815-C with 818-SL detector). The light intensity was first measured 25 mm in front of the LED concentrator lens, first for the royal blue and neutral white LEDs separately, and then with all LEDs combined for maximum intensity. At this distance, the concentrator lens provides a 12 mm beam diameter with the other optical components removed for the baseline measurement. The light intensity was then measured at the light guide entrance (with a 6.6 mm diameter aperture to mimic the opening of the light guide) and at the output of the cable to determine the efficiency of the optics and the cable itself. The intensity was measured as a function of distance from the end of the light guide to determine the acceptable working distance.

SECTION III

RESULTS

A. Light Intensity—The baseline light intensity for blue and white LEDs combined was determined to be $13.1 \mu\text{W}/\text{cm}^2$. With the additional optical components in place, $7.3 \mu\text{W}/\text{cm}^2$ of combined light was captured within the 6.6 mm diameter aperture designed to mimic the opening of the light guide, a 44% loss when coupling the light from the concentrator lens to the much smaller light guide entrance. Light intensity was also measured as a function of distance from the end of the light guide, as shown in Figure 4. As the working distance increases, the combined intensity declines from 0.26 to $0.02 \mu\text{W}/\text{cm}^2$, with an ideal working distance of less than 10 mm. The low intensity values observed may be the result of damage to the donated light guide utilized (see Discussion).

B. QD Excitation and Visualization—An earlier version of this prototype has been used to detect QD-labeled tissue in an artificial surgical environment [23]. Figure 5 shows example visualization. $\sim 27 \text{ mm}^3$ chicken tissue samples were non-specifically labeled with a QD solution of 250nM or 500nM. The samples were viewed using a standard clinical rigid thoracoscope, with an earlier version of the prototype as a light source. The top images show the unfiltered emission; some red regions are visible on the 500nM sample, but are barely visible on the 250nM sample. The lower images show the filtered emission, and the red labeling is clearly visible. These preliminary results demonstrate that using the proposed device, QD emissions from labeled tissue are visible through an endoscope, and that these emissions can distinguish labeled tissue from non-labeled surroundings.

SECTION IV

DISCUSSION

We present a prototype LED light source that can be used with a clinical endoscope to view QD-labeled tissue. It provides QD excitation light and white light for surgical cavity illumination, while maintaining low cost, compact size, and low power consumption. The

system is modular in design, allowing for part interchangeability to accommodate different situations and easy implementation of improvements. In this implementation, the LEDs of each color are connected in series for uniformity of brightness, simplicity, and compatibility with a single BuckPuck DC driver per circuit. The DC drivers provide constant current regardless of voltage or number of LEDs operated, making the system easy to modify. Alternatively, the LEDs may be connected in parallel to lower the required voltage. The prototype was built for under 350 USD, excluding costs associated with 3D printing, making this a low-cost alternative to commercial endoscope light sources.

During the evaluation process, several shortcomings were identified that may be addressed in future iterations to improve the efficiency of the light source. While some loss in light intensity was anticipated, approximately 44% loss was measured between the concentrator lens and the light guide entrance. This could be improved by using a reflector tube or larger lenses capable of capturing more scattered light. Additionally, 98% of the light intensity was lost between the concentrator lens and the exit of the light guide. There are two hypothesized causes for this dramatic loss. First, it was discovered that the donated fiber optic cable is damaged, with numerous small cracks on both ends. Thus, a properly functioning light guide will be necessary for future work. Second, the convergence angle may be steeper than the theoretical calculation due to combined alignment error between the optical components, causing the majority of the light to fall outside of the acceptance angle of the cable, which is relatively small for long cables such as that employed in this study. This may be addressed by placing an additional biconcave lens between the aspheric condensing lens and the light guide. This would provide collimated light at the cable's entrance and decrease the convergence angle, making the device compatible with a wider variety of light guides. The circuitry may also be modified to better match the demands of the system. For instance, the current may be increased to match the maximum rated drive current of the LEDs and increase their brightness. Additionally, resistors may be used in place of the BuckPuck DC drivers to save space and cost, at the expense of interchangeability. While 9V batteries were chosen for convenience, portability, and price, alternative power sources could be employed to allow for longer procedures. Finally, the LEDs selected for this iteration of the device can be replaced to match the excitation wavelengths of other QDs or fluorophores, rendering the device plausible for human use with currently FDA approved fluorophores. Finally, higher illuminance LEDs could be utilized, though the increased heat generation of such LEDs must then be balanced.

Future experiments and iterations of the prototype will measure performance and functionality in clinical scenarios. Ultimately, this device serves as a step towards the long-term goal of incorporating QDs into routine image-guided surgical procedures.

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Fig. 1.

Illustration of optical components designed to efficiently couple LED excitation light with the light guide. A minimal convergence angle and distance is desirable. Not to scale.

Fig. 2.

A sample circuit diagram for a royal blue LED. A similar circuit was used for the neutral white LEDs. The current light source design features two separate circuits with 4 royal blue and 3 neutral white LEDs in series.

Fig. 3.
Prototype device, showing rapid-prototyped base (green), optics and circuitry. Distances between components increased for better visibility

Fig. 4.
Light intensity as a function of distance from exit of light guide.

(A) [250nM] un-filtered; blue LED. Red fluorescence is barely visible.

(B) [500nM] un-filtered; blue LED. Slight red fluorescence visible.

(C) [250nM] filtered; blue LED. Slight red fluorescence is visible.

(D) [500nM] filtered; blue LED. Red fluorescence is clearly visible.

Fig. 5.

Un-filtered and filtered QD-labeled tissue samples (~27 mm³ in volume) illuminated with blue LED.