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Visualization of Contrast-Enhanced Intraoperative Optical Coherence Tomography with Indocyanine Green

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Summary

Optical coherence tomography (OCT) based visualization of ophthalmic anatomy has transformed the clinical practice of ophthalmology. The translation of OCT into the surgical theater is currently being actively researched and may provide a paradigm shift in surgical practice. Enhanced visualization of tissues and tissue planes may provide further iterative improvement in surgeon feedback. Contrast enhanced intraoperative OCT (λ OCT) has been previously described with triamcinolone. In this report, we describe the OCT features and contrast enhancement noted with indocyanine green utilizing λ OCT in human subjects as well as an *ex vivo* analysis in porcine eyes.

Introduction

Optical coherence tomography (OCT) has changed the detection and management of pathology in ophthalmology.¹ Intraoperative OCT (λ OCT) is an emerging field that holds similar promise of enhanced visualization of surgical pathology and OCT-assisted surgical decision-making.²⁻⁶ In many imaging modalities (e.g., CT, MRI), the use of contrast agents can improve tissue visualization and pathology detection. Generally, the use of OCT contrast agents in ophthalmology has been lacking. The application of contrast agents during λ OCT could potentially enhance surgeon feedback and visualization of tissues of interest during surgical procedures.⁷⁻⁹

As previously described, agents such as triamcinolone, prednisolone, and lipid-based artificial tears allow for enhanced visualization of translucent microstructures in both *in-vivo* and *ex-vivo* contrast-enhanced OCT imaging.⁷⁻⁹ In this report, we describe the OCT properties of indocyanine green (ICG, IC-Green, Akorn, Lake Forest, IL) as an λ OCT contrast agent for ophthalmic surgery.

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Methods

iOCT Clinical Surgical Analysis

A retrospective consecutive case series of eight eyes with iOCT imaging following placement of ICG was performed. IRB approval was obtained and the study adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants for surgical intervention and for iOCT.

Intraoperative imaging was performed using a custom microscope-mounted iOCT system with a portable spectral domain OCT probe (Bioptigen; Research Triangle Park, NC). A standardized imaging protocol was utilized with volume scanning performed over a 10×10 mm area with 100 B-scan scans per area at both 0 and 90 degrees. Preincision scans were performed. Prior to membrane peeling, ICG was utilized to stain the internal limiting membrane (ILM) and/or epiretinal membrane (ERM) and iOCT was performed.

Quantitative analysis of the changes in reflectivity in the pre- and post-ICG scans was performed with ImageJ software. Using a standardized area with the polygonal measurement tool, a series of images for each eye was evaluated and a mean intensity was measured. Measurements were taken at the ILM+/- ERM and the nerve fiber layer (NFL). An OCT contrast ratio was calculated by dividing the mean intensity of the ILM layer by the mean intensity of the NFL layer. This measurement was made for both pre- and post-contrast scans. A Wilcoxon rank-sum test was used to compare the OCT contrast ratios between the pre and post-contrast images.

Ex Vivo Analysis

Quantitative image analysis was performed on fresh cadaveric porcine eyes following application of three contrast agents [ICG, triamcinolone (Triesence, Alcon, Fort Worth, TX), and 1% prednisolone acetate]. Imaging was performed with a portable spectral domain OCT system (Bioptigen). All procedures were performed in triplicate. A fresh porcine eye was initially imaged without contrast (e.g., artificial tears) and then imaged after 1-2 drops of contrast solution was placed on the cornea surface. Intracorneal measurements were also performed. A 2.8 mm keratome clear-corneal incision was made in the peripheral cornea and imaged without contrast material. The clear corneal incision was then stained with the contrast agent and imaged. Contrast enhancement was evaluated at various planes including on the corneal surface (topical) and within the corneal wound (intracorneal). OCT contrast ratio was calculated as outlined above

Results

Quantitative analysis of iOCT images pre and post-contrast instillation using ICG revealed a significant difference in reflectivity at the ILM/ERM. The mean contrast ratio in the pre-contrast eyes was 0.907 and 1.42 in the post-ICG eyes ($p < 0.001$). Qualitatively, smooth contrast enhancement was noted at the level of the ILM with increased hyperreflectivity (Figure 1). Increased shadowing was also noted in some areas below the ICG (Figure 2).

Qualitative analysis of fresh porcine eyes showed a smooth contrast enhancement ICG with underlying shadowing (Figures 3A-B; 4A-B). Triamcinolone provided a granular appearance with irregular shadowing noted below the contrast agent. (Figures 3C-D; 4C-D). Prednisolone acetate provided a uniform contrast enhancement with less shadowing compared to triamcinolone and ICG (Figures 3E-F 4E-F). Quantitative analysis revealed an intra-wound contrast ratio of 1.26 for the control, 1.58 with ICG, 1.72 with triamcinolone, and 1.69 with the prednisolone (all $p < 0.01$). Analysis of topical application showed similar relative changes in contrast ratio with control (1.00), ICG (1.20), triamcinolone (1.51), and prednisolone (1.23) (all $p < 0.01$).

Discussion

In vivo contrast-enhanced OCT remains a nascent field. Use of different OCT contrast agents have been previously reported including prednisolone, lipid-based artificial tears, and triamcinolone with promising results.⁷⁻⁹ In our review of the literature, this represents the first description of the *in vivo* OCT properties of ICG used during a surgical procedure. This increased reflectivity, however, came with decreased visualization of the tissues below the ICG contrast. The relative changes noted on OCT could be potentially utilized in future integrated λ OCT systems to facilitate ILM identification.¹⁰⁻¹²

Qualitative analysis of the various agents' reflectivity profile in both topical and intracorneal applications of ICG compared to triamcinolone revealed a smooth versus granular contrast profile, respectively. Both agents appeared to have significant shadowing in the underlying tissues. Interestingly, prednisolone acetate allows for adequate contrast of both the tear film and corneal wounds with decreased subjective shadowing of sub-contrast structures when compared to ICG and triamcinolone. The reflectivity profiles visualized for triamcinolone and prednisolone mirror our previously published results on contrast-enhanced OCT.⁷⁻⁹

This study does have important limitations, including its small size and retrospective nature. Further prospective research is needed to better understand the potential role of ICG-enhanced OCT-based visualization of ocular structures during λ OCT. The portable SD-OCT system utilized in this system is limited in its ability to target to areas of interest. Future studies with integrated λ OCT systems may provide increased information on the real-time changes that occur with ICG staining in the OCT signal and reflectivity profile of the tissues of interest.

The implications of this contrast agent in the future of λ OCT contrast enhancement remain to be seen. In other areas of medicine, contrast enhancement for imaging modalities have resulted in significant iterations in disease visualization and diagnosis. The use of contrast agents during λ OCT may provide an important surgeon feedback and enhance understanding of tissue planes and architecture, perhaps resulting functional feedback regarding tissue dynamics.⁷⁻⁹

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Figure 1. Intraoperative OCT images in pre- (A) and post-indocyanine green (ICG, B) contrast enhancement of the internal limiting membrane (ILM) using ICG in a case of vitreomacular traction with a full-thickness macular hole. Note the increased visibility of ILM post-ICG contrast instillation (arrow).

Figure 2.

(A) Intraoperative OCT (iOCT) pre-indocyanine green (ICG) image of epiretinal membrane (yellow arrow). (B) iOCT image of the epiretinal membrane following application of ICG. Notice the increased relative reflectivity (red arrow) at the level of the epiretinal membrane with significant shadowing of the retina below (*).

Figure 3.

Ex vivo B-scan OCT images of porcine cornea. Control images (A, C, E) with artificial tears showing no alterations in reflectivity in the precorneal area (yellow arrows). (B) Post-contrast enhancement with topical indocyanine green (ICG) with increased reflectivity (orange arrows) compared to artificial tears. (D) Post-contrast enhancement with topical triamcinolone showing granular increased hyperreflectivity (orange arrows). (F) Post-contrast enhancement with topical prednisolone with smooth hyperreflectivity (orange arrows) with less comparative shadowing.

Figure 4.

Ex vivo B-scan OCT images of porcine cornea following creation of corneal incision. Control images (A, C, E) with slight increased reflectivity in area of the corneal wound (yellow arrows). (B) Post-contrast wound enhancement with topical indocyanine green (ICG) with increased reflectivity (orange arrows) compared to control with significant underlying tissue shadowing (red arrow). (D) Post-contrast wound enhancement with topical triamcinolone showing granular increased hyperreflectivity (orange arrows) and significant underlying shadowing (red arrow). (F) Post-contrast enhancement with topical prednisolone with smooth hyperreflectivity (orange arrows) with less comparative shadowing (red arrow) compared to ICG and triamcinolone.