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Intrasurgical Assessment of Subretinal tPA Injection for Submacular Hemorrhage in the PIONEER study Utilizing Intraoperative OCT

Justis P. Ehlers¹, Daniel S. Petkovsek¹, Alex Yuan¹, Rishi P. Singh¹, and Sunil K. Srivastava¹

¹Ophthalmic Imaging Center, Cole Eye Institute, Cleveland Clinic

Abstract

Purpose—To assess the feasibility of intraoperative OCT (iOCT) during pars plana vitrectomy with subretinal tissue plasminogen activator (tPA) injection for subretinal hemorrhage.

Methods—Eyes that underwent vitrectomy and subretinal injection of tPA were identified from the PIONEER study, a prospective clinical study assessing the feasibility and utility of iOCT in ophthalmic surgery. A microscope mounted spectral domain OCT system (Bioptigen SDOIS) was utilized for iOCT imaging. A standardized scan protocol and image acquisition was followed for intraoperative imaging.

Results—iOCT was successfully obtained in 4/4 eyes. In all cases, increased subretinal fluid was noted with differential reflectivity visualized between the hemorrhage/tPA interface confirming appropriate localization of tPA injection. Image quality variability was significant.

Conclusions—iOCT can successfully be performed during PPV with subretinal tPA injection. Utilizing iOCT, appropriate placement of tPA solution and corresponding retinal architectural changes were visualized.

Introduction

The management of neovascular age-related macular degeneration (NVAMD) has been revolutionized by the advent of vascular endothelial growth factor (VEGF) inhibitors (e.g., ranibizumab, aflibercept, bevacizumab).¹⁻³ Anti-VEGF therapy is the gold standard for the management of most NVAMD complications. Significant submacular hemorrhage (SMH), however, remains a devastating complication of NVAMD. Some cases of SMH may be amenable to surgical intervention with pars plana vitrectomy (PPV) and hemorrhage displacement. The use of tissue plasminogen activator (tPA) has been reported as a surgical adjunct administered both intravitreally and in the subretinal space.⁴⁻⁷

Corresponding Author: Justis P. Ehlers, Cole Eye Institute, Cleveland Clinic, 9500 Euclid Ave/i32, Cleveland OH 44195. Phone: 216-318-7129. ehlersj@ccf.org.

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When administered in the subretinal space, a transretinal approach is utilized to deliver tPA to the appropriate anatomic location. The microarchitectural alterations that occur during this process are unknown. Intraoperative optical coherence tomography (iOCT) has been described in multiple vitreoretinal surgical diseases, including macular hole, optic pit maculopathy, vitreomacular traction, and retinal detachment.⁸⁻¹⁴ Many of these studies have identified significant microarchitectural changes that occur following surgical manipulation, some of which appear to have significant prognostic value.⁹⁻¹¹

To our knowledge, iOCT has not been previously described in procedures involving subretinal injections. In this study, we assess the feasibility of iOCT during PPV with subretinal tPA for SMH in NVAMD and assess the utility of iOCT in identifying retinal alterations that may occur during subretinal placement of tPA.

Methods

The PIONEER study is a prospective multi-surgeon study examining the use of iOCT in ophthalmic surgery. This study represents an analysis of eyes within the PIONEER study that were treated with PPV and subretinal tPA for extensive SMH secondary to NVAMD. This study was approved by the Cleveland Clinic Foundation (CCF) Institutional Review Board (IRB) and all tenets of the Declaration of Helsinki were followed. Informed consent was obtained from all patients. Preoperative, intraoperative, and postoperative clinical variables were collected, including age, visual acuity, intraocular pressure, surgical procedure information, and imaging data.

Surgical Procedure

All patients underwent standard 3-port PPV for subretinal injection of tPA. Following vitrectomy, tPA (25 mcg/0.1 mL or 0.25 mg/mL) was injected into the subretinal space utilizing a 41 gauge transretinal needle in three of four cases, while an incisional retinotomy with subsequent subretinal cannulation with a 32 gauge cannula was utilized in the other case (Case 1). A subretinal bleb was created to in order to bathe the entire clot and to allow for optimal displacement of the hemorrhage. Following tPA injection, a partial air-fluid was performed and an air-gas exchange was performed with sulfur hexafluoride (SF₆). Following initial supine positioning, patients were then instructed to maintain an upright posture.

iOCT Scanning System and Analysis

Utilizing a custom, microscope-mounted system, the Bioptigen Envisu SDOIS (Bioptigen, Research Triangle Park, NC) portable probe was attached to the ophthalmic microscope, as previously described.⁹⁻¹¹ According to the PIONEER protocol, iOCT was performed at various surgical milestones as determined by the surgeon, including preincision and following tPA injection. A preset image acquisition protocol was utilized, including cubic 10 × 10 mm volume scans (at 0 and 90 degrees) and 10 mm radial volume scans. Each scan consisted of 100 B-scans distributed across the area with 1000 A-scans per B-scan. All scanning sequences were exported for image analysis. Qualitative analysis was performed by two independent reviewers.

Results

Four eyes of four patients were identified within the PIONEER study that underwent vitrectomy and subretinal tPA injection with concurrent iOCT imaging. Successful iOCT imaging was obtained in 4 of 4 (100%) cases. The case descriptions and imaging features are included below.

Case 1

A 76 year old female undergoing anti-VEGF therapy for NVAMD. She presented with significant subfoveal hemorrhage with visual acuity (VA) of hand motion only. Preoperative SD-OCT revealed significant subretinal fluid with dense SMH adhering to the subretinal surface and loss of foveal depression. Central subfield thickness (CST) was 355uM. PPV and placement of subretinal tPA (0.4 mL) was performed with 16% SF6 gas displacement. Pre-incision and post-tPA injection iOCT scans were successfully obtained. Pre-incision iOCT confirmed the sub-macular location and inferior extension of the hemorrhage, and the lack of a prominent sub-RPE component. Post-tPA iOCT revealed increased subretinal fluid with differential reflectivity visualized between the hemorrhage/tPA interface confirming appropriate localization of tPA injection (FIGURE 1). The size and distribution of the tPA bleb could be visualized utilizing multiple scans. A possible retinal defect site was noted on one of the scans that may correspond to the location of the retinotomy (FIGURE 1). No iOCT or surgical complications occurred. The patient remained on anti VEGF therapy with monthly injections for 3 months post-operatively. BCVA reached 20/150 at 6 months post-operatively and CST was 165uM.

Case 2

A 78 year old male with NVAMD treated with anti-VEGF therapy presented with severe SMH. Pre-operative VA was 20/300, and CST was 256uM. Pre-operative SD-OCT revealed a large SMH with foveal disruption, modest subretinal fluid and localized sub-RPE component. PPV was performed. Subretinal tPA injections (0.1ml) were performed with (16% SF6) gas displacement. Pre-incision and post-tPA injection iOCT scans were successfully obtained. Pre-incision scans revealed a submacular hemorrhage extending nearly completely over the area of RPE detachment.. Post-tPA scans revealed differential reflectivity of the hemorrhage-tPA interface and dramatically increased subretinal fluid (FIGURE 2). Two injections were performed, and retinal disruption that was consistent on multiple scans indicated both a probable needle track and injection site (FIGURE 2). No iOCT or surgical complications were reported. Following continued anti-VEGF therapy, BCVA was 20/100 at final follow up at 13 months and CST was 253 uM.

Case 3

An 87 year old female with NVAMD undergoing anti-VEGF therapy presented with a large submacular hemorrhage. Prior to surgery, VA was 20/200 with CST of 286 uM. Pre-operative SD-OCT revealed widespread submacular hemorrhage with subretinal fluid and RPE detachment (FIGURE 3). PPV with subretinal tPA injections at two sites was performed with 20% SF6 gas displacement. Pre-incision and post-tPA injection iOCT scans were successfully obtained. Pre-incision scans confirmed the extent of the hemorrhage and

the absence of a significant sub-RPE component. Post-tPA injection scans revealed subtle hemorrhage-tPA interface differential reflectivity, with increased subretinal fluid temporal to the fovea (FIGURE 3). Potential transretinal needle tracks were not clearly identified. No surgical complications were reported. Post-operative BCVA was count fingers at 3 feet. BCVA was 20/50 one year postoperatively with a CST of 248 μ M.

Case 4

Case 4 is a 64 year-old female with a history of glaucoma and NVAMD who presented emergently with a large submacular hemorrhage and extensive inferior hemorrhagic detachment. Pre-operative VA was 20/400. PPV with subretinal tPA injections at two locations were performed with 20% SF6 gas displacement. Pre-incision and post-tPA injection iOCT scans were successfully obtained. Pre-incision scans were of limited quality particularly due to the bullous-nature of the inferior hemorrhagic retinal detachment (FIGURE 4). Post-tPA injection scans revealed a large hemorrhage with a clear tPA-hemorrhage interface. The postoperative course was complicated by full-thickness macular hole and retinal detachment, though the hemorrhage had resolved. Two months following successful surgical repair of the retinal detachment and macular hole, visual acuity was 20/400 with associated recurrent SMH CST was 189 μ M.

Discussion

Toxins, retinal traction and shearing, and impaired diffusion between the retina and RPE stemming from SMH contribute to rapid photoreceptor degeneration and vision loss.¹⁵ Vitrectomy and subretinal injection of tPA with pneumatic displacement of hemorrhage has shown promise as a surgical intervention for this complication of NVAMD.⁷ In this case series, three of the four patients had significant improvement in functional and anatomic parameters. Intraoperative visualization of the retinal architecture following tPA injection may improve understanding of this technically demanding surgery and potentially impact technique. It is known that appropriate localization of the cannula is critical. The retina is approximately 250 microns thick and isolating the plane between the retina and retinal pigment epithelium (RPE) can be difficult in cases with a shallow hemorrhagic retinal detachment. Intraretinal or sub-RPE injection of tPA is not only ineffective but can have negative consequences. Identifying the ideal location for needle penetration is also challenging and real-time iOCT-guidance in the future could potentially facilitate appropriate site selection.

In numerous vitreoretinal conditions, iOCT has demonstrated the ability to visualize the impact of surgical maneuvers on the retinal architecture and potentially improve our understanding of the pathophysiology of vitreoretinal surgical diseases.⁸⁻¹² In this study, iOCT was successfully obtained at multiple surgical time points with minimal disruption to the surgeon. The imaging demonstrates alterations in the reflectivity profile of the subretinal hemorrhage following tPA administration and successfully demonstrates appropriate localization of the tPA in the subretinal space. Additionally, in select cases, alterations were identified that suggested potential areas of previous retinal penetration which have already showed tissue apposition.

This study has several limitations. The small sample size limits significant quantitative and comparative data analysis. However, the rarity of this procedure makes enrolling a large number of patients difficult. Image quality was also highly variable, likely due to the significant hemorrhagic component of this disorder with variable shadowing. Optimal aiming to the area of interest was also challenging due to the non-integrated nature of the *i*OCT system utilized for this study and variability among the various surgeons.

Future studies could include real-time visualization of needle placement through using a microscope-integrated OCT system providing immediate feedback to the surgeon.¹⁶⁻¹⁸ Additionally, quantitative analysis of subretinal fluid volume and optimization of injection speed/volume may also be feasible. Volumetric assessment of architectural alterations identified during *i*OCT have been previously demonstrated.¹¹ In the future, visualization with real-time *i*OCT may also facilitate the refinement of techniques to deliver pharmacologic agents or biologics precisely to a specified surgical plane.

This report demonstrates the feasibility of *i*OCT during PPV with subretinal tPA injection. Utilizing *i*OCT, appropriate placement of tPA solution was visualized in the subretinal space. Architectural changes, such as potential needle track location, are also visualized with *i*OCT. We believe this report represents the first description of *i*OCT visualization of subretinal drug delivery during surgical intervention.

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Figure 1.

Case 1. Preoperative OCT (A) with large area of submacular hemorrhage. Intraoperative image (B) demonstrating extensive subretinal hemorrhage. Intraoperative OCT B-scans (C, D, E) with subretinal hemorrhage highlighted in yellow (C, D, E), which is displaced after tissue plasminogen activator (tPA) injection (D). The new hyporeflective bleb is highlighted in red (D, E). Subretinal fluid with differential reflectivity between the hemorrhage/tPA interface can be visualized (D, E). Subretinal cannulation was achieved with a localized retinotomy and area of increased hyperreflectivity is noted temporally in an area of bullous detachment that may correspond to retinotomy site (green outline). Follow-up OCT is shown at 8 months (F) with the resolved subfoveal fluid and subretinal hemorrhage.

Figure 2.

Case 2. Intraoperative OCT (iOCT) B-scans (A,B,C). Pre-incision iOCT (A) revealed a submacular hemorrhage extending nearly completely over an area of smaller retinal pigment epithelium (RPE) detachment. Subretinal hemorrhage is highlighted in yellow (A). Post-tPA iOCT scans revealed a large amount of increased subretinal fluid without increased sub-RPE component confirming appropriate location of tissue plasminogen activator injection (B,C). The white arrows (B, C) indicate disturbances in the retinal architecture that may reflect transretinal needle tracks. Follow-up OCT is shown at 13 months (D) with resolution of subretinal hemorrhage and significantly decreased subretinal fluid.

Figure 3.

Case 3. Preincision intraoperative OCT (iOCT) B-scan (A) reveals subfoveal hemorrhage, highlighted in yellow. Following tissue plasminogen activator (tPA) injection (B), iOCT identifies area of increased subretinal fluid (red, orange) secondary to subretinal delivery of tPA. (C) Follow-up OCT at 1 year shows reduced subfoveal hemorrhage with outer retinal atrophy and persistent subretinal tissue.

Figure 4.

Case 4. Preoperative OCT (A) revealing extensive subretinal hemorrhage and retinal elevation with associated intraretinal fluid. Preincision intraoperative OCT (iOCT) B-scan (A) shows limited quality with bullous retinal detachment with visualization of inverted retinal tissues due to retinal height (white arrows). Following tissue plasminogen activator (tPA), interface (yellow arrows) between hyporeflective subretinal fluid and hyperreflective hemorrhage is visualized. (C) Follow-up OCT at 2 months shows retinal pigment epithelium tear with improved subretinal hemorrhage.