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Utility of Anterior Segment OCT Measurements for Predicting Severe Eye Pressure Increase after Intravitreal Dexamethasone Implant

Michael A Singer[1], Angela Herro[2], Joshua Singer[1], Krishna Surapaneni[2], Jason Espitia[1] and William E Sponsel[3]*

[1]*Medical Center Ophthalmology Associates (MCOA), San Antonio, Texas, USA*

[2]*University of Texas Health Science Center, San Antonio, Ophthalmology, Texas, USA*

[3]*University of Texas San Antonio, Biomedical Engineering and WESMDPA Glaucoma Service, San Antonio, Texas, USA*

Abstract

Background/aims: To assess the utility of non-contact anterior segment ocular coherence tomography (AS-OCT) measurement of the angle recess width (AR) to predict eyes prone to intraocular pressure (IOP) spikes after injection of intravitreal dexamethasone implant in patients with CRVO and BRVO.

Methods: Cohort study with fellow-eye control of 34 patients with gonioscopically open angles and RVO undergoing intravitreal injection of dexamethasone implant (Ozurdex). All participants received pre-injection AS-OCT in both eyes using spectral domain Cirrus OCT. Independent masked assessors measured the AR width using electronic imaging calipers. IOP was monitored prior to implant placement, and monthly for 6 months thereafter. Comparisons between AR width and degree of steroid response, phakic status, gender, and prior history of glaucoma were analyzed.

Results: Seven eyes (20%) developed severe IOP spikes (IOP ≥ 30 mmHg). There was a highly significant (p=0.0085) difference in angle recess width between severe responders (175.0 ± 27.1 μm) and those eyes with less severe response (272.9 ± 24.3 μm). There was also strong correlation between the AR width in study and fellow eyes (mean 248.1 ± 19.8 vs. 261.9 ± 22.6 μm; R2=0.67).

Conclusions: This study reaffirms the potential utility of AS-OCT measurement of AR width as a practical means for helping identify eyes at high risk of ocular hypertension after intravitreal corticosteroid administration.

Keywords: Anterior segment ocular coherence tomography; Intraocular pressure; Angle recess; Dexamethasone; Intravitreal implant; Steroid response; OCT; Ozurdex; Glaucoma; Retina

Abbreviations: AR: Angle Recess; OCT: Ocular Coherence Tomography; RVO: Retinal Vein Inclusion; BRVO: Branch Retinal Vein Inclusion; ASOCT: Anterior Segment Ocular Coherence Tomography

Introduction

Recent evidence suggests that the propensity for steroid induced IOP elevation may be related to the macroscopic narrowness of the angle approach, as measured by performing radially oriented measurements of the approach to the outflow angle using noncontact anterior segment optical coherence tomography (AS-OCT) [1]. Peak postoperative intraocular pressures were found to vary inversely with the width of the gap separating the most anteriorly-prominent peripheral iris fold from the corneal endothelium. The circumferential space encompassed between this pre-goniotic iridocorneal narrowing and the anatomic angle is known as the 'angle recess' [1]. A narrow angle recess (AR) entry (<200 microns) appears to be associated with a high risk for severe eye pressure increase after intravitreal triamcinolone injection. Time domain OCT imaging was used in the initial studies demonstrating this association [1]. The present study was conducted to see if a similar association might hold after surgical placement of a dexamethasone intravitreal implant, using spectral domain technology to assess the angle recess. An assessment of any possible effects of pre-existing pseudophakia or a prior history of eye pressure increase or glaucoma was also carried out.

Steroids are widely used in ophthalmology, via topical, subconjunctival, intravitreal, and oral administration. All forms may produce elevation of IOP in certain patients [2-7]. Ozurdex dexamethasone intravitreal implants were approved by the FDA in 2009 for treatment of central (CRVO) and branch retinal vein occlusion (BRVO). Subsequently the implant was approved for treatment of noninfectious uveitis, and has since been used discretionarily for a wide range of ophthalmic inflammatory conditions.

In a study conducted by Lowder et al. [8], dexamethasone intravitreal implants were effective in reducing intraocular inflammation and improving visual acuity during a 6 month follow-up among patients with noninfectious intermediate and posterior uveitis. Across all study visits ~10% of patients with intravitreal dexamethasone implants attained at least one post-injection IOP level ≥ 25 mmHg, among whom half attained an IOP ≥ 35 mmHg [8]. Combined clinical trial results from other retinal vein occlusion and uveitis studies showed that ~15% of patients experienced at least a 10 mmHg IOP increase after a single Ozurdex injection, and ~20% after two injections [9].

Most clinically significant eye pressure increase arises a month or more after initiation of steroid therapy [10]. From a practical perspective, predicting which eyes might develop a steroid-associated ocular hypertensive response is difficult. For some ophthalmologists this might discourage use of dexamethasone inserts for patients who

***Corresponding author:** Prof. William Sponsel, University of Texas San Antonio, Biomedical Engineering and WESMDPA Glaucoma Service, 311 Camden Street, Suite 306, San Antonio, TX 78215, USA, Tel: 210-223-9292; Fax: 210-223-9266; E-mail: sponsel@earthlink.net

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might otherwise benefit from a controlled release steroid implant, particularly among patients with any history of eye pressure increase. Such concerns might be obviated if some practical means to help predict which patients might be more prone to develop pressure spikes could be found.

Because steroid-induced IOP elevation is typically associated with a gonioscopically open angle, it has been generally assumed that any obstruction to outflow must lie within the trabecular outflow system itself. In an effort to identify a causative factor, Johnson, Bradley and Ascot performed titrated-glucosamine radiolabeling studies on human trabecular cell culture, and after lysis and fractioning found that undigestible glycosaminoglycan (GAG) levels were nearly doubled after 2-3 weeks of dexamethasone treatment [11]. Metabolically derived undigestible GAG is translucent, thus invisible on gonioscopy, and has viscoelastic properties similar to the commercial sodium hyaluronate glycosaminoglycans used in cataract surgery. All cataract surgeons know the potential effects of retained viscoelastic on postoperative IOP. The intrinsic surface tension of these agents may create the potential for a circumferential gasket-like seal of a totally open and otherwise unobstructed angle. It may be that microscopically these derivatives collect within weeks of initiation of steroid therapy, however it may take additional weeks to month to become clinically evident or significant. It is thus plausible that, regardless of the intrinsic state of the trabecular meshwork itself, a circumferentially narrow angle approach might promote any tendency for metabolically derived GAG to coalesce and accumulate, retarding aqueous flow into the angle from the anterior chamber.

Methods

This is a retrospective, IRB-approved study of patients treated with the dexamethasone intravitreal implant (Ozurdex®, Allergan, Irvine, CA) from 2009 to 2012 in eyes with a diagnosis of either branch retinal vein occlusion or central retinal vein occlusion. Patients with open angle glaucoma were included in this study group to comparatively assess their relative tendency to develop severe eye pressure increase, and to explore whether any IOP elevation among that subgroup might arise more independently of the angle recess measurement than the non-glaucomatous eyes. All known glaucoma patients were medically controlled on topical therapy, had normal intraocular pressure at the time of Ozurdex injection, and remained on the same pre-injection topical antiglaucoma regimen thereafter. None had any clinical evidence of retinal vein occlusion (RVO) associated rubeosis iridis.

In all patients the Dexamethasone implant (Ozurdex) injection was performed as an eye was administered 1 ml of subconjunctival lidocaine for anesthesia. The 0.7 mg dexamethasone (Ozurdex) implant was then injected intravitreally 3.5-4.0 mm posterior to the limbus. Topical quinolone antibiotic was applied immediately thereafter.

Intraocular pressure measurements were recorded prior to implant placement, and then monitored at bi-monthly intervals over a 6-month period post-injection. All patients underwent comprehensive eye exams prior to initiating treatment, and all study eyes were confirmed to have open angles by gonioscopy. To test the practical utility of AR measurement from a straightforward clinical perspective, two simple groups of interest were compared – those with IOP rise at any point post-injection greater than or equal to 30 mmHg (higher risk IOP) and those consistently maintaining IOP<30 mmHg (lower risk IOP). The baseline characteristics of the angle recess were compared between these two groups. The baseline IOP of each patient's paired eyes were obtained by using the Goldmann applanation measurements taken immediately before the dexamethasone implant (Ozurdex) injection. These were then compared to corresponding IOP levels after injection, and gauged for an increase in IOP. During each follow up visit IOP was recorded one time by an experienced technician naïve to the study objectives.

The angle recess was measured using separate imaging software after importing the spectral-domain image from the OCT and converting the overall image dimensions into microns using standard scan acquisition conversion software. Then a caliper tool was used to measure the angle recess (AR) entry (defined as the shortest axis between the anterior-most prominence of the iris root and the posterior cornea) (Figure 1). Both the treated eye and the non-treated fellow eye were measured by two independent observers masked to all clinical parameters. Mean AR values were documented, paired eye and inter-observer angle recess measurement correlations were calculated by linear regression, and statistical differences between peak post-insertion IOP categories among eyes with and without prior ocular hypertensive history or pseudophakia were determined using non paired t-tests.

Results

Thirty-four eyes of 34 patients underwent pars plana insertion of a dexamethasone intravitreal (Ozurdex) implant in one eye (13 eyes of 13 male subjects, and 21 eyes of 21 female subjects). At baseline, 20 (57%) of the eyes had a documented history of open angle eye pressure increase. All of these were satisfactory controlled on conservative topical medical therapy, and all continued their existing topical regimen throughout the pre- and post-injection study interval. Twenty-one eyes (62%) were pseudophakic (Table 1).

Eight of the 34 study eyes (23.6%) had AS-OCT AR measurements of <200 μ. Four of these 8 eyes (50%) developed IOP spikes ≥ 30 mmHg ($p<0.001$). These four eyes constituted 75% of the 6 total eyes attaining that high-risk IOP level at any point throughout the study period. All six were from among the 20 eyes with a known prior history of eye pressure increase, constituting 30% of that subgroup. Among the 6 eyes attaining high-risk IOP, 4 (67%) were pseudophakic, half with AR width values <200 μm (Figure 2).

The mean number of days from dexamethasone intravitreal implant (Ozurdex) injection to intraocular pressure spike was 52 ± sem 5.4 days (range 40-69 days). There was a strong correlation between the study and fellow eye OCT angle recess (AR) measurement values (mean treated eye AR 248.1 ± sem 19.8 μm; mean non-treated fellow eye AR

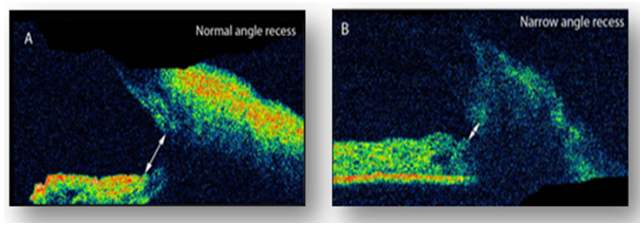

Figure 1: Stratus OCT image of normal angle recess (1A) versus narrow angle recess (1B).

Baseline demographics: preponderant subgroups	
Female	21 (62%)
Glaucoma	20 (59%)
Pseudophakic	21 (62%)

Table 1: Baseline demographics.

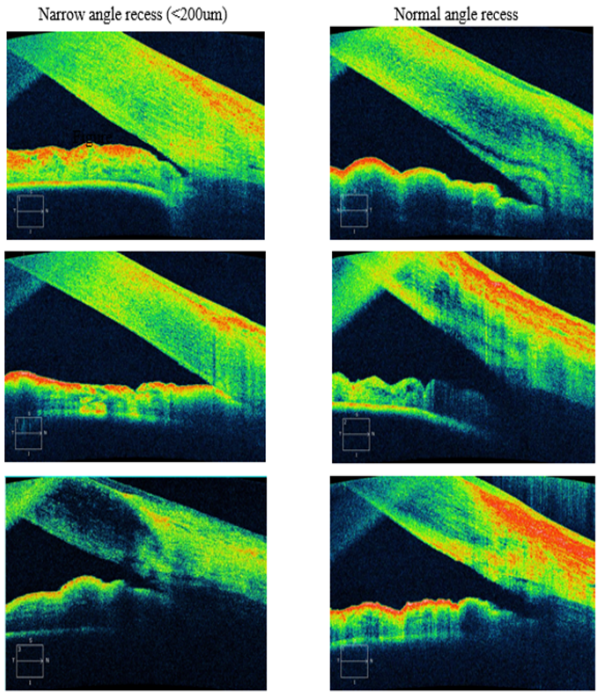

Figure 2: Examples of narrow and normal angle recesses using the Cirrus OCT imaging of the anterior segment. Narrow angle recesses are those with aperture<200 µm.

Category	Mean angle recess (µm)		p-value
Gender	Male: 235.6	Female: 245.94	0.429
Glaucoma	Glaucoma: 246.2	No glaucoma: 264.3	0.35
Phakia	Phakic: 175.5	Pseudophakic: 299.2	0.0064

Table 2: Differences in angle recess in baseline demographics.

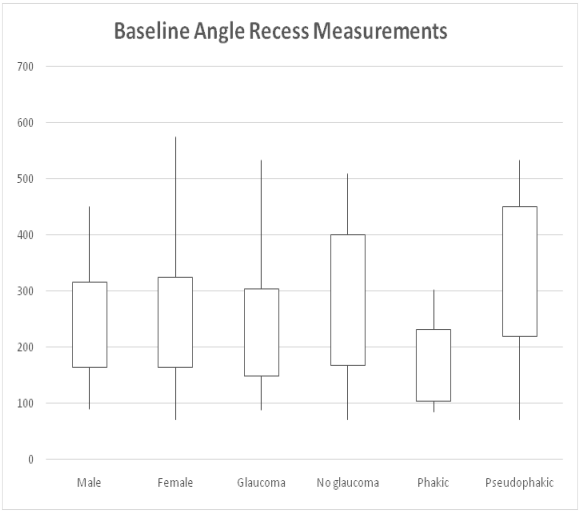

Figure 3: Baseline angle recess measurements with range plots. Only the difference between phakic and pseudophakic angle recesses at baseline was found to be significantly different.

261.9 ± 22.6 µm; R2=0.67). There was also a strong linear correlation between the two masked observers' measurements of AR width for both eyes of each subject (R2=0.69). There was no significant increase in IOP noted among the non-treated fellow eyes during the course of the study.

There was a statistically significantly difference in baseline AR characteristics between phakic and pseudophakic eyes using composite data for both the treated and non-treated eyes of all subjects (phakic eyes (n=22) mean AR 175.5 ± 22.2 µm and pseudophakic eyes (n=46) mean AR 299.2 ± 27.8 µm; p=0.0064. There was, however, no significant difference in AR between men and women (p=0.668), or between patients with or without a prior history of eye pressure increase (p=0.35; Table 2 and Figure 3).

Among all study subjects, eyes developing a high-risk IOP response ≥ 30 mmHg were more likely to have a narrow angle recess, and this was highly statistically significant (175 ± 27 µm vs. 273 ± 24 µm, p=0.0085; Table 4). Eyes developing an IOP rise ≥ 30 mmHg after implantation were significantly more likely to have had prior OHT than those that did not (p=0.02; Table 3), although the majority (14; 70%) of previously ocular hypertensive eyes did not exhibit any high risk IOP spike after dexamethasone injection. The overall range and mean AR among the eyes with a prior OHT history did not differ significantly from that of the total study group. Four of the 6 eyes with high-risk IOP elevation were pseudophakic, 2 with an AR<200 µm and 2 with an AR>200 µm. Both of the phakic eyes developing high-risk IOP had an AR width<200 µm.

Discussion

This study expands upon previous work in several ways: (1) it employs more up-to-date spectral domain imaging rather than time domain AS-OCT; (2) it evaluates a recently introduced dexamethasone intravitreal implant (prior study assessed triamcinolone acetonide injections); (3) it includes eyes with a known pretreatment tendency for eye pressure increase; and (4) it seeks clinical relevance rather than mere statistical AS:IOP associations by imposing an arbitrary "high-risk" IOP cutoff of ≥30 mmHg.

A narrow opening to the angle recess of <200 µm was strongly associated with severe IOP elevation (IOP ≥ 30 mmHg) during the immediate 6-month post-operative period after injection with the dexamethasone (Ozurdex®) implant. These data are consistent with prior study data demonstrating a strong correlation between the angle recess width and IOP response after intravitreal triamcinolone injection [1]. In the present study however, more eyes at baseline had a pre-existing history of eye pressure increase in association with their branch and central retinal vein occlusion. It is reassuring that Ozurdex implantation was not associated with high-risk IOP levels arising among any of the 14 eyes that did not already have a known predilection for eye pressure increase. It is also interesting to note that although pseudophakia was generally associated with a significantly wider mean AR, pseudophakia *per se* did not preclude the possibility of individuals having a very narrow AR width or high-risk IOP elevation.

These results reinforce the suggestion that imaging the angle recess using spectral domain OCT technology might be a noninvasive, rapid and reproducible method that could contribute toward the detection of eyes at greatest risk for clinically relevant post-steroidal IOP spikes. Eyes exhibiting a prominent circumferential fold in the pre-trabecular peripheral iris which narrows the angle approach to <200 µm on AS-OCT appear to be at highest risk for post-steroidal IOP elevation. This association appears to hold among eyes with a prior history of eye pressure increase receiving dexamethasone implants as it did in an earlier study among eyes receiving triamcinolone [1]. This narrow noncontact AS configuration is somewhat akin to plateau iris, often a subtle sign on clinical gonioscopy that can easily be lost via inadvertent

Category	IOP<30 mmHg (n=28)	IOP ≥ 30mmHg (n=6)	p-value
Male	9	4	0.12
Glaucoma	14	6	0.02
Phakic	11	2	0.79

Table 3: Demographic differences between responders and non-responders.

IOP (mmHg)	Number, n=34 (%)	Mean AR width (μm)
≥30	6 (18%)	175 ± 27 sem
<30	28 (82%)	263 ± 24 sem

Table 4: Comparison of angle recess width in two groups of patients: IOP<30 mmHg and IOP ≥ 30 mmHg. P-0.0085.

gonio compression. It is reasonable to postulate that the narrower the AR, the greater the risk that gradual accumulation of high-viscosity metabolic by-products of intraocular steroid might directly obstruct the angle approach, or alter the relative surface tension characteristics of the iris and corneal endothelium and induce occult intermittent angle closure.

There was a significant difference in the AR width between phakic and pseudophakic eyes, the latter having a substantially wider AR. Although pseudophakic eyes exhibited an apparent trend toward lower peak IOP values after injection, this association was not statistically significant, nor was pseudophakia evidently clearly protective against a severe IOP response. Indeed, among the twenty eyes with a pre-existing diagnosis of glaucoma, only two of the six phakic eyes produced pressure spikes ≥ 30 mmHg (33%; mean AR 126.3 μm), compared with four of the fourteen pseudophakic eyes (29%; mean AR 218.4 μm).

In the prior study looking at IOP after triamcinolone injection [1], it was found that an angle recess of <200 μm may be a convenient and readily-remembered cutoff below which a patient may be at substantially higher risk for developing a steroid response after an intravitreal injection. The present study reaffirmed that an angle recess width of 175 ± 24 μm (<200 μm) was strongly associated with a severe IOP response as seen in prior study examining eye that had increased IOP after triamcinolone injection [1]. Thus, using the 200 μm AR as a cutoff threshold may help risk-stratify patients into two categories. Those with such narrow angle recesses might benefit from more frequent post-operative follow up visits, IOP checks, and prophylactic therapy. This could be in the form of anti-glaucomatous topical therapy, or possible laser treatment of the angle region[A] .

Regardless of underlying physiologic mechanisms, a practical AS-OCT indicator that could help clinicians prevent post-steroidal ocular hypertensive morbidity might be of considerable clinical value. If AR narrowing is a causative association, prophylactic treatments like SLT or argon trabeculoplasty to widen the angle approach might be of future benefit to patients found to be at risk[B]. Further studies are required to determine to what extent AS-OCT might actually help enhance the beneficial use of intravitreal steroids to treat ocular inflammation and edema.

[A]Realini T (2010) Is There a Role for SLT in Managing Steroid-Related OHT? Glaucoma Today.

[B]Singer M, et al. (2012) How SLT Affects the Angle: A Three-Dimensional View. Association for Research in Vision and Ophthalmology Annual Meeting, Fort Lauderdale, FL, USA.

Conflict of Interest

Authors have no competing interest in the work presented here.

Contributorship Statements

Michael Singer, MD is responsible for discovering the angle recess association with intraocular pressure elevation, the initial conception and design, as well as critical revision of the article for intellectual content, and has given final approval of the version to be published.

Angela Herro, MD is responsible for contributions to conception and design, acquisition of data and analysis and interpretation of data, as well as drafting the article for intellectual content. She has given final approval of the version to be published.

Joshua Singer is responsible for acquisition of data, and drafting or revising the article critically. He has given final approval of the version to be published.

Jason Espitia is responsible for contributions to conception and design, acquisition of data and analysis and interpretation of data, drafting the article, and has given final approval of the version to be published.

William Sponsel, MD is responsible for substantial contributions to conception and design, drafting and revising the article critically for intellectual content and has given final approval of the version to be published.

References

1. Singer MA, Groth SL, Sponsel WE, Herro A, Pollard J, et al. (2013) Association of OCT angle recess width with IOP response after intravitreal triamcinolone injection. Retina 33: 282-286.
2. Garrott HM, Walland MJ (2004) Glaucoma from topical corticosteroids to the eyelids. ClinExpOphthalmol 32: 224-226.
3. Kalina RE (1969) Increased intraocular pressure following subconjunctival corticosteroid administration. Arch Ophthalmol 81: 788-790.
4. Smithen LM, Ober MD, Maranan L, Spaide RF (2004) Intravitreal triamcinolone acetonide and intraocular pressure. Am J Ophthalmol 138: 740-743.
5. Singh IP, Ahmad SI, Yeh D, Challa P, Herndon LW, et al. (2004) Early rapid rise in intraocular pressure after intravitreal triamcinolone acetonide injection. Am J Ophthalmol 138: 286-287.
6. Gillies MC, Simpson JM, Billson FA, Luo W, Penfold P, et al. (2004) Safety of an intravitreal injection of triamcinolone: results from a randomized clinical trial. Arch Ophthalmol 122: 336-340.
7. Becker B (1965) Intraocular pressure response to topical corticosteroids. Invest Ophthalmol 4: 198-205.
8. Lowder C, Belfort R Jr, Lightman S, Foster CS, Robinson MR, et al. (2011) Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. Arch Ophthalmol 129: 545-553.
9. Haller JA, Bandello F, Belfort R Jr, Blumenkranz MS, Gillies M, et al. (2010) Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology 117: 1134-1146.
10. Jones R 3rd, Rhee DJ (2006) Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature. CurrOpinOphthalmol 17: 163-167.
11. Johnson DH, Bradley JM, Acott TS (1990) The effect of dexamethasone on glycosaminoglycans of human trabecular meshwork in perfusion organ culture. Invest Ophthalmol Vis Sci 31: 2568-2571.