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Ocular Side Effects Associated with Peribulbar Injections of Triamcinolone Acetonide for Diabetic Macular Edema

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Abstract

Purpose—To evaluate long term effects of anterior and posterior peribulbar injections of triamcinolone acetonide (TA) on intraocular pressure (IOP) elevation and cataract development.

Methods—This study reports on IOP and cataract progression through 2 years in 96 eyes with diabetic macular edema (DME) randomized to focal/grid photocoagulation, 20mg TA anterior injection, anterior injection followed by laser, 40mg TA posterior injection, or posterior injection followed by laser.

Results—IOP increased from baseline by 10 mmHg at 1 visit through 2 years in 2 (8%) eyes in the laser group, 11 (31%) eyes in the anterior groups, and 6 (17%) eyes in the posterior groups. Among phakic eyes at baseline, 0, 5 (17%), and 1 (3%) in the 3 groups respectively underwent cataract surgery prior to the 2-year visit.

Conclusions—Based on this small randomized trial, it appears that over 2 years anterior peribulbar TA injections are associated with an increased incidence of IOP elevation and an increased risk of cataract development compared with laser or posterior peribulbar injections. The association of posterior injections with IOP elevation is less certain. Although the study involved eyes with DME, the results should be relevant to other conditions treated with peribulbar corticosteroids.

Introduction

Peribulbar injections of corticosteroid have been used in the treatment of a number of ocular conditions, such as diabetic macular edema (DME),^{1, 2} cystoid macular edema following cataract surgery, and most commonly uveitis.^{3–7} We conducted a phase 2 randomized trial

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that evaluated anterior and posterior peribulbar injections of triamcinolone acetonide, either alone or in combination with focal/grid photocoagulation, compared with focal/grid photocoagulation alone for treatment of DME associated with relatively good visual acuity.⁸ The results of this study showed that peribulbar injections did not have substantial beneficial effects compared with focal/grid photocoagulation. The cohort was followed through 2 years, which provided the opportunity to obtain additional safety data for peribulbar corticosteroid treatment. This information may be useful not only in the management of DME but also for other conditions for which peribulbar corticosteroids are used.

Methods

The study protocol has been described previously and baseline characteristics have been reported.⁸ This study included 129 eligible eyes with DME of 109 subjects. Each study eye was assigned randomly to 1 of 5 treatments including: 1) focal/grid laser photocoagulation (n=38), 2) anterior peribulbar (presumably sub-Tenon) injection of 20 mg triamcinolone acetonide (Kenalog; Bristol-Myers Squibb, New York, NY) (n=23), 3) anterior peribulbar (presumably sub-Tenon) injection of 20 mg triamcinolone acetonide followed by focal/grid laser photocoagulation at the 4-week follow-up (n=25), 4) posterior peribulbar (presumably sub-Tenon) injection of 40 mg triamcinolone acetonide (n=21), or 5) posterior peribulbar (presumably sub-Tenon) injection of 40 mg triamcinolone acetonide followed by focal/grid laser photocoagulation at the 4-week follow-up (n=22). Participants with bilateral involvement were assigned randomly to laser photocoagulation in one eye and to 1 of the other 4 treatment groups in the other eye. By protocol, all subjects had a baseline intraocular pressure (IOP) measurement ≤ 24 mm Hg. The peribulbar injection was repeated after 17 weeks if DME was still present. After the primary outcome at 34 weeks, treatment was at the investigator's discretion. Follow-up visits were completed at 1 and 2 years. IOP was measured at each visit using a Goldmann tonometer. In phakic eyes, the lens was assessed on slit lamp examination for nuclear sclerotic, cortical, and posterior subcapsular changes based on the Age-Related Eye Diseases Study (AREDS) standard lens photographs which classified the cataract as absent, present less than a standard photograph, or present greater than or equal to a standard photograph at baseline, 4 months, 8 months, and annually.⁹

The triamcinolone acetonide injection techniques were standardized and based on investigator usual practices. At investigator discretion, subconjunctival lidocaine 1% could be used for anesthesia. Using a 27-gauge 5/8 inch needle, the anterior injection of 20 mg triamcinolone acetonide was given beneath the bulbar conjunctiva and tenon under the lower lid at the junction of the bulbar and palpebral conjunctiva and the posterior injection of 40 mg of triamcinolone acetonide was given in the subtenon's space of the superior temporal quadrant about 10 mm posterior to the limbus.

Statistical Methods

To address this paper's objective, eyes that received treatment for DME other than that of the randomized assignment or focal/grid photocoagulation were not included in the analyses. Eyes receiving systemic or study eye corticosteroid treatment for reasons other than DME also were not included. In addition, one eye without any follow-up visits was not included. As a result, the cohort for analysis included 35 eyes that were treated with anterior peribulbar triamcinolone acetonide injections (15 treated with one, 14 two, and 6 three injections), 36 treated with posterior peribulbar triamcinolone acetonide injections (16 treated with one, 14 two, and 6 three injections), and 25 treated with laser photocoagulation alone.

Treatment group comparisons for binary IOP and lens progression outcomes were assessed using repeated measures generalized estimating equations (GEE) models accounting for the

correlated data from subjects with 2 study eyes. Odds ratios and 2-sided 95% confidence intervals(CI) were determined from GEE logistic regression models where appropriate. For outcomes with no events in a treatment group, Fisher's exact test was used to compare treatments.

Cumulative probabilities of an increase in IOP of at least 10 mm Hg or IOP lowering medication being prescribed were calculated using the Kaplan-Meier method. The proportional hazards model was used to compare treatment groups. A robust sandwich estimate of the covariance matrix was used to account for correlation within subjects who had 2 study eyes.¹⁰ Statistical analyses were conducted using SAS version 9.1 software (SAS Institute Inc., Cary, NC).

Results

The median ages of the participants in this cohort were 56 years for the 25 eyes in the laser group, 61 years for the 35 eyes in the anterior injection group, and 65 years for the 36 eyes in the posterior injection group. The participants with an eye in the laser group were 88% white, 4% black, and 8% Asian; those in the anterior injection group were 83% white, 11% black, 3% Hispanic, and 3% other; and those in the posterior injection group were 81% white, 14% black, 3% Hispanic, and 3% Asian.

Two-year follow up was completed for 22 (88%) of 25 eyes in the laser group, 28 (80%) of 35 in the anterior injection group and 26 (72%) of 36 in the posterior injection group. There were 5 deaths, all in the posterior injection group.

Increased Intraocular Pressures (IOP)

As seen in Table 1, IOP was increased from baseline by ≥ 10 mm Hg at one or more visits in 2 eyes (8%) in the laser group, 11 eyes (31%) in the anterior injection group, and 6 eyes (17%) in the posterior injection group; reaching 30 mm Hg or higher in 0, 7 (20%), and 3 (8%) eyes in the 3 groups, respectively. One (4%), 9 (26%), and 5 (14%) eyes in the 3 groups, respectively, were treated with IOP-lowering medications at some point. Compared with the laser group, the odds ratio for an increase in IOP ≥ 10 mm Hg or treatment with IOP-lowering medications was 4.2 (95% CI 1.2 to 14.9) in the anterior injection group and 1.9 (95% CI 0.5 to 7.4) in the posterior injection group. The odds ratio in the anterior injection group compared with the posterior injection group was 2.3 (95% CI 0.8 to 6.4). Figure 1 shows the time to either an increase in IOP of ≥ 10 mm Hg or treatment with IOP-lowering medications in each group ($P = 0.03$ for comparison of laser group with anterior injection group, $P = 0.30$ for comparison of laser group with posterior injection group, and $P = 0.15$ for comparison of anterior injection group with posterior injection group). No eyes had glaucoma surgery during the study.

Progression of Lens Opacity or Cataract Extraction

Among phakic eyes at baseline, 0 of 24 in the laser group, 5 (17%) of 30 in the anterior injection group, and 1 (3%) of 29 in the posterior injection group underwent cataract surgery prior to the 2-year visit ($P = 0.06$ for the anterior injection group compared with the laser group, $P = 1.00$ for the posterior injection group compared with the laser group, and $P = 0.19$ for the anterior injection group compared with the posterior injection group). All 5 cataract surgeries in the anterior injection group occurred after the 1-year visit following one injection in 1, two injections in 2, and three injections in 2. In the posterior injection group the one eye had cataract surgery between the 34-week visit and the 1-year visit following one injection. Table 2 (online website) shows the clinical lens assessment at 2 years in phakic eyes compared with the baseline assessment. Cataract extraction by 2 years or

worsening on clinical lens assessment by 1 or more standards at 2 years occurred in 6 (27%) eyes in the laser group, 16 (62%) eyes in the anterior injection group, and 8 (38%) eyes in the posterior injection group among phakic eyes at baseline for subjects completing the 2-year visit ($P = 0.02$ for comparison of laser group with anterior injection group, $P = 0.38$ for comparison of laser group with posterior injection group, and $P = 0.24$ for comparison of anterior injection group with posterior injection group).

Development of Ptosis

In addition to elevated IOP and cataract formation, ptosis was noted in our previous report of the original cohort in 3 (6%) of 48 eyes that received an anterior injection, 5 (12%) of 43 eyes that received a posterior injection, and none of the 38 eyes receiving laser alone.⁸ Since the first report, there has been 1 additional case of ptosis identified in the posterior injection group, approximately 7 months after the second and final injection.

Discussion

We evaluated the adverse effects of IOP elevation and cataract development following peribulbar triamcinolone acetonide injections for DME. Injections were given in a standardized manner.⁸ Follow up was completed prospectively and was longer than previously reported studies.^{2, 11}

The sample size was too small for definitive statistical analyses. However, the results suggested that the anterior peribulbar injections were associated with an increased incidence of IOP elevation and more substantial cataract formation compared with the laser control group or posterior peribulbar injections. The association of posterior peribulbar injections with increased IOP is less certain. The results suggest that these adverse effects may not be seen until the second year of follow-up, thus, demonstrating the importance of long term follow up of an eye that receives peribulbar corticosteroid injections. The use of the anterior sub-Tenon approach is not common and, to our knowledge, its associated adverse effects have rarely been discussed in the literature, especially the development of ptosis. Several reports have described low frequencies of IOP elevation and cataract development after posterior steroid injections. However, most of these studies have had less than 6 months or one year of follow up.^{1, 2, 12, 13}

The risk of IOP elevation and cataract progression is higher in the anterior peribulbar group compared with the posterior peribulbar group. This may be due to the fact that steroid-induced glaucoma is associated with increased outflow resistance at the trabecular meshwork.¹⁴ The anterior location of the depot of triamcinolone acetonide makes it much more accessible to the area of outflow resistance as well as close proximity to the lens. Resection of the anterior deposit of steroids has been demonstrated to decrease the IOP almost immediately.¹⁵ Although not evaluated in this study, drug reflux following posterior subtenon injection has been demonstrated in another study to predict an increase in intraocular pressure.¹⁶

A theoretic rationale for using the anterior and posterior sub-Tenon injections was that the adverse effects would be less than those associated with intravitreal injections of triamcinolone acetonide. In a DRCR.net-conducted study of intravitreal injections of triamcinolone acetonide (4 mg) for DME, the 2-year incidence of cataract surgery was 51%, which appears higher than the incidence with peribulbar injections from the current study.¹⁷ However, the 2-year incidence of IOP elevation in the anterior injection group was similar to the incidence in the intravitreal triamcinolone acetonide study, where the incidence of IOP elevation 10 mm Hg was 33%, with 30% requiring IOP lowering medications.¹⁷

In summary, based on these results, it seems likely that the risk of IOP elevation and cataract development is increased with anterior peribulbar triamcinolone acetonide injections and greater than the risk with posterior peribulbar injections while ptosis development is increased with the posterior peribulbar injections. Although the study involved eyes with DME, the results should be relevant to other conditions that are treated with peribulbar corticosteroids.

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The most recently published list of the Diabetic Retinopathy Clinical Research Network investigators and staff can be found at www.drctr.net.

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Figure 1.

Kaplan-Meier analysis of cumulative probability of intraocular pressure (IOP) change ≥ 10 mm Hg or IOP-lowering medication prescribed at any visit. The “# eyes at risk” indicates the number of eyes still in follow up at the beginning of the interval that have not previously met the IOP outcome. The “# outcome” indicates the number of eyes with IOP change ≥ 10 mm Hg or IOP-lowering medication prescribed for the first time during the subsequent time interval. Data from eyes with incomplete follow up were censored at the last completed visit.

Table 1

Intraocular Pressure During Follow Up by Treatment Group

	Anterior Injection Group	Posterior Injection Group	Laser Group
	N (%)	N (%)	N (%)
Baseline	N=35	N=36	N=25
IOP 21–24 mm Hg	1 (3%)	4 (11%)	0
17 Weeks	N=35	N=35	N=25
IOP 21–29 mm Hg	12 (34%)	6 (17%)	0
IOP 30 mm Hg	1 (3%)	0	0
Increase from baseline 10 mm Hg	3 (9%)	0	0
IOP-lowering medications being used	0	1 (3%)	0
34 Weeks	N=32	N=32	N=25
IOP 21–29 mm Hg	6 (19%)	3 (9%)	2 (8%)
IOP 30 mm Hg	1 (3%)	1 (3%)	0
Increase from baseline 10 mm Hg	2 (6%)	2 (6%)	0
IOP-lowering medications being used	2 (6%)	0	1 (4%)
1 Year	N=31	N=30	N=25
IOP 21–29 mm Hg	6 (19%)	1 (3%)	2 (8%)
IOP 30 mm Hg	2 (6%)	2 (7%)	0
Increase from baseline 10 mm Hg	3 (10%)	2 (7%)	0
IOP-lowering medications being used	3 (10%)	0	0
2 Years	N=28	N=26	N=22
IOP 21–29 mm Hg	2 (7%)	1 (4%)	2 (9%)
IOP 30 mm Hg	0	0	0
Increase from baseline 10 mm Hg	0	0	0
IOP-lowering medications being used	6 (21%)	3 (12%)	0
Occurrence at Any Visit	N=35	N=36	N=25
IOP 30 mm Hg	7 (20%)	3 (8%)	0
Increase from baseline 10 mm Hg	11 (31%)	6 (17%)	2 (8%)
IOP-lowering medications being used	9 (26%)	5 (14%)	1 (4%)

IOP= Intraocular Pressure

Table 2
Lens Gradients at 2 Years for Phakic Eyes at Baseline by Baseline Lens Grading (website only)

Lens Opacity at 2 Year Visit Based on Clinical Exam				
	N	Cataract Extraction	Absent	Present < standard
Baseline Lens Grading Based on Clinical Exam^a				
Nuclear Sclerosis				
Treatment – Laser				
Absent	2	0	0	2
Present < standard	18	0	2	15
Present standard	2	0	0	1
Treatment – Anterior				
Absent	2	0	1	1
Present < standard	19	4	1	12
Present standard	5	1	0	1
Treatment – Posterior				
Absent	3	0	0	3
Present < standard	14	0	1	11
Present standard	4	1	0	1
Cortical				
Treatment – Laser				
Absent	8	0	6	2
Present < standard	12	0	3	8
Present standard	2	0	0	1
Treatment – Anterior				
Absent	11	1	6	4
Present < standard	11	3	4	3
Present standard	4	1	0	1

Lens Opacity at 2 Year Visit Based on Clinical Exam				
	N	Cataract Extraction	Absent	Present < standard
Treatment – Posterior				
Absent	8	0	8	0
Present < standard	11	1	0	9
Present standard	2	0	0	0
Posterior Subcapsular				
Treatment – Laser				
Absent	18	0	18	0
Present < standard	3	0	2	0
Present standard	1	0	1	0
Treatment – Anterior				
Absent	24	5	14	4
Present < standard	2	0	1	0
Present standard	0	0	0	0
Treatment – Posterior				
Absent	18	0	14	4
Present < standard	2	0	1	1
Present >= standard	1	1	0	0

^aPhakic eyes only