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Intraocular Pressure Control for Patients Undergoing Combination Intravitreal Anti-VEGF and Dexamethasone Therapy for Macular Edema from Retinal Vein Occlusion

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Abstract

Background and Objective: Sustained-release dexamethasone intravitreal implant is an effective treatment for macular edema secondary to retinal vein occlusion (RVO) but ocular hypertension is a side effect. This study evaluated whether the addition of a single combination IOP-lowering medication will reliably control intraocular pressure (IOP) for those patients.

Study Design/Patients and Methods: Retrospective chart review of 62 patients that underwent multiple injections of combination anti-VEGF and sustained-release dexamethasone intravitreal implant for macular edema secondary to RVO. IOP spikes were treated with brimonidine 0.2% - timolol 0.5%. IRB approval was obtained.

Results: The average elevated IOP requiring treatment was 28.6 mmHg. The average IOP after adding brimonidine 0.2% - timolol 0.5% was 16.7 mmHg. 100 percent of treatment cycles had an IOP < 30 mmHg after starting treatment. Conclusions: Using one combination IOP-lowering drop can reliably control the ocular hypertension that occurs secondary to combination therapy for macular edema in RVO.

Keywords: Anti-VEGF, Dexamethasone, Intraocular pressure, Macular edema, Retinal vein occlusion, Ocular hypertension

Abbreviations: RVO: Retinal Vein Occlusion; CRVO: Central Retinal Vein Occlusion; BRVO: Branched Retinal Vein Occlusion; IOP: Intraocular Pressure; VEGF: Vascular Endothelial Growth Factor

Background and Objective

Macular edema secondary to retinal vein occlusion (RVO) is a common cause of vision loss in older persons, the second most common retinal vascular disease after diabetic retinopathy, affecting sixteen million persons worldwide [1]. It is caused by occlusion of retinal veins by vascular clot, external compression, or vessel wall pathology [2]. There are two distinct types, classified according to the site of occlusion. Occlusion can occur either in the central retinal vein (CRVO) or branches of the retinal veins (BRVO) that combine to form the central vein. Both BRVO and CRVO are associated with significant impairments in vision-related quality of life (as measured by the National Eye Institute visual function questionnaire, NEI-VFQ) [3]. Secretion of vascular endothelial growth

factor (VEGF) can cause fluid leakage from capillaries draining into the obstructed vein, resulting in edematous thickening of the retina [2]. Macular edema is the most common cause of vision loss from RVO [1]. First-line treatment is with anti-VEGF agents.

BRAVO, CRUISE, and multiple other studies have shown that using Ranibizumab to treat BRVO and CRVO is effective at increasing visual acuity (>15 letters at 6 months for best corrected visual acuity) and decreasing central foveal thickness [4].The safety profile for giving injections of Ranibizumab was consistent with previous phase III trials and no new safety events were identified [4].

Intravitreal Aflibercept has also been successful in the treatment of macular edema secondary to RVO with an increase in best-corrected visual acuity and decreased foveal thickness as shown in the VIBRANT, GALILEO, and COPERNICUS studies [5-7]. No new safety events were seen in these studies.

Corticosteroids, including dexamethasone, are known to have anti-inflammatory and anti-angiogenic properties that may inhibit the expression of VEGF and other pro-inflammatory cytokines [1]. Intravitreal implantation of sustained-release dexamethasone is an effective treatment for BRVO and CRVO with improvement in best-corrected visual acuity. Unfortunately, it has been linked to an increase in intraocular pressure (IOP). The highest percentage of patients with an IOP increase to > 25 mmHg was observed at day 60 [8]. This trend has been well documented in the literature, 45% of patients developed ocular hypertension (>22 mmHg) in the 12 weeks after dexamethasone treatment was initiated [9]. Another study noting that the proportion of patients requiring treatment for increased IOP rose from 6% to 24% following initiation of dexamethasone therapy [1].

Recent investigations into combination anti-VEGF and dexamethasone implant therapy suggest that the two treatment options may act synergistically. A recent prospective case study compared the effects of combination Bevacizumab and dexamethasone therapy versus dexamethasone alone in patients with either central or branch RVO. Combination therapy was associated with an increased visual acuity and a prolonged time between injections when compared with either of these medications alone [10]. In a study comparing monotherapy with intravitreal dexamethasone versus combination therapy with anti-VEGF, 23.8% of the patients receiving monotherapy versus 34.6% in the combination group had an IOP > 10 mmHg from baseline. Twenty-five percent in the monotherapy group versus 37% in the combination group had an IOP > 25 mmHg. Six percent versus 10.7% had an IOP > 35 mmHg. 2.4% of the patients required glaucoma surgery [11].

The purpose of the present study is to demonstrate that the addition of brimonidine 0.2% - timolol 0.5% drops is an effective therapy in mitigating the IOP increase following administration of subsequent intravitreal anti-VEGF and dexamethasone combination therapy for RVO.

Study Design/Patients and Methods

This retrospective study reviewed the charts of 62 patient eyes, which underwent multiple injections of combination intravitreal anti-VEGF and intravitreal dexamethasone for macular edema secondary to retinal vein occlusion (RVO) from September 2009 to June 2014. IRB approval was obtained prior to chart review. The primary outcome was IOP changes over time. IOP was followed for all patients during the course of the study, extending to 51 months. The treatment protocol for macular edema was administration of an intravitreal anti-VEGF followed 2 weeks later by intravitreal dexamethasone. This comprised the start of the first treatment cycle. Patients were then monitored for decreased visual acuity of more than 6 Snellen chart letters, an increased thickness on OCT of more than 50 microns from their baseline, or more than 300 microns overall. If they met one of these criterions, they were retreated with an intravitreal anti-VEGF and then 2 weeks later with intravitreal dexamethasone. This represented cycle 2. Patients were followed for a total of 6 cycles. Patients with an IOP spike were treated with brimonidine 0.2%-timolol 0.5% (combigan). The baseline elevated IOP was recorded and compared to post-combigan treatment IOP spikes for all time points as well as monthly comparisons extending to 12 months.

Results

Twenty-four of 62 eyes (38.7%) had an IOP greater than or equal to 23 mmHg at least once. 30.6% of eyes had an IOP greater than or equal to 25 mmHg. 17.7% had an IOP greater than or equal to 30 mmHg. Three of 62 (4.8%) eyes had an IOP greater than or equal to 35 mmHg. Ten of 62 eyes were treated with brimonidine-timolol combination drops. The average pre-treatment IOP for these patients requiring IOP lowering drops was 28.6 mmHg. The post-treatment IOP for these patients

ranged from 13.7 to 18.5 mmHg with a mean of 16.7 mmHg (Figure 1). After starting brimonidine-timolol combination drops, the IOP remained stable over time (Figure 2). 73.7% of the patients had a maximum IOP less than 23 mmHg, 89.5% with a maximum IOP of less than 25 mmHg, and 100% with a maximum IOP of less than 30 mmHg. 80% of the secondary IOP elevations while on brimonidine-timolol combination drops occurred within 4 months of initiating treatment; 60% occurred within the first month of initiating treatment.

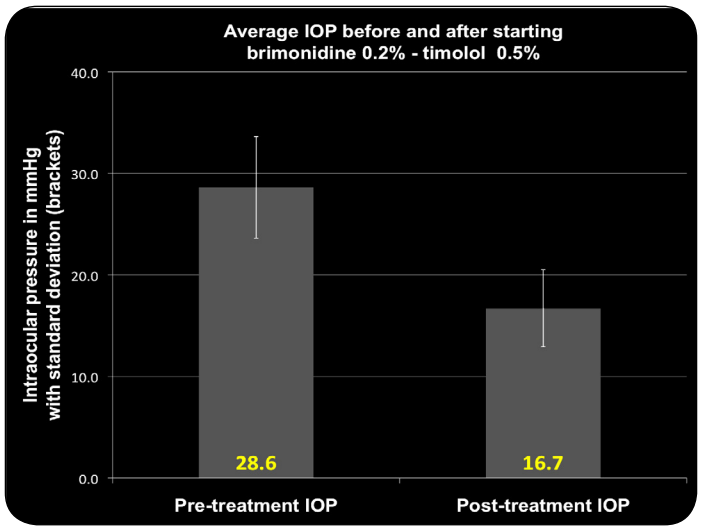

Figure 1: Average IOP before and after starting combination topical therapy.

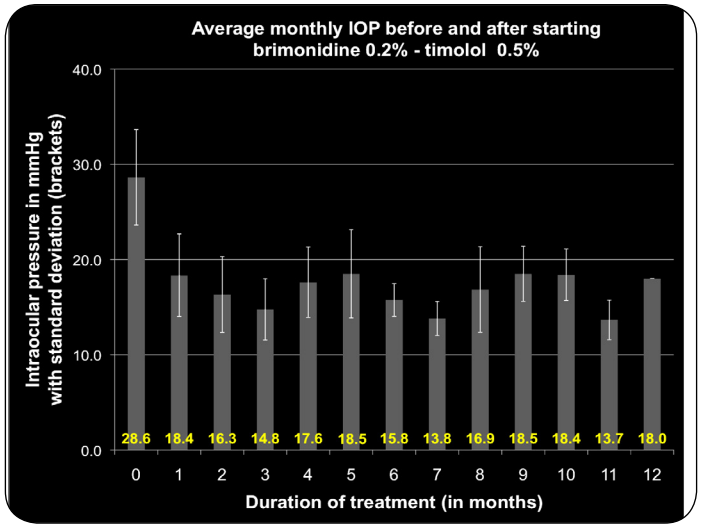

Figure 2: Average IOP before combination topical therapy (month 0) and over time after initiation of topical therapy.

Discussion

Intravitreal anti-VEGF agents work well, but combination therapy with intravitreal dexamethasone also has a role in the treatment of macular edema secondary to retinal vein occlusions. Elevation in intraocular pressure is a known side effect of any steroids including intravitreal dexamethasone, which can cause hesitation to use it despite it being an effective treatment option. The above referenced studies showed an average of 29% of patients will have an IOP > 25 mmHg or 10 mmHg above baseline. Recent data showed that following multiple injections of intravitreal dexamethasone, 53% had an IOP greater than or equal to 23 mmHg; 42% with IOP great than or equal to 25 mmHg; and 11% greater than or equal to 30 mmHg [12]. The SAFODEX study evaluated ocular hypertension secondary to intravitreal dexamethasone when used for all etiologies. 28.5% of the patients had an IOP greater than or equal to 25 mmHg or > 10 mmHg above baseline IOP. 6% had an IOP > 35 mmHg. Most importantly, 97% of the cases were controlled using topical medication alone. 3% required oral medication and only 0.7% required filtration surgery [13]. Another study reported IOP elevation > 10 mmHg from baseline or > 25 mmHg in 8.6% of patients at month 1 and 25% at month 4 [14]. In a UK study, 12% of patients had an IOP > 25 mmHg, 11% required medical therapy for elevated IOP, and 1.2% required glaucoma filtering surgery for control of IOP [15]. Our study showed similar findings with an incidence of 30.6% for ocular hypertension, which was controlled using one combination IOP-lowering medication.

Conclusions

Ocular hypertension is a well-documented side effect of steroid use. Yet, intravitreal dexamethasone is an effective treatment for retinal vein occlusions and can be reliably controlled with one combination IOP-lowering topical medication. Further studies need to be conducted to identify patients that may be more at risk for steroid-response ocular hypertension with the goal of prevention and/or early treatment.

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Financial Disclosures/Conflicts of Interest for Dr. Bell: Alcon, Optos, Aerpio, Ampio, Regeneron, Allergan, Genentech

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