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Resident Perspectives 55—2

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Effect of 6-week washout period on intraocular pressure following chronic prostaglandin analogue treatment

Jenny Qian, PGY-1

The reduction of intraocular pressure (IOP) is currently the only proven strategy for treating open-angle glaucoma (OAG).[1] Generally, the initial target is a 20% to 50% decrease in IOP, however, target levels vary depending on pretreatment pressures associated with retinal damage, severity of damage, risk factors for progression, life expectancy, and potential treatment adverse effects.[2] Various classes of topical medications are available to lower IOP, including prostaglandin analogues (PGAs). Due to their effectiveness and few systemic side effects, monotherapy with PGAs is often the first line of treatment. PGAs increase aqueous humour outflow though the uveoscleral pathway, thereby decreasing outflow resistance and IOP.[3,4] They are administered once daily, but there is evidence to suggest their usage over a prolonged period can provide sustained benefits even after discontinuation.[5–8] In this issue, Lim et al. investigated whether the IOP-lowering effects of chronic PGA use persist after discontinuation.[9]

Eighty-seven patients (154 eyes) with OAG or OAG suspects on monotherapy PGA for ≥ 6 months who achieved ≥ 20% IOP reduction from baseline were enrolled in this prospective, single-blinded, parallel, single-centre, randomized controlled clinical trial. Of these, 48 participants (85 eyes) were randomized to the "washout" group, which discontinued PGA therapy, and 39 participants (69 eyes) were randomized to the control group, which continued PGA therapy. Baseline demographics, including pretreatment IOPs, were comparable between groups. They were followed for 6 weeks and IOP was measured at days 0 (day of randomization), 7, 21, and 42.

The primary objective was to evaluate the effect of the washout period on IOP after chronic PGA use. The authors discovered there was a significant difference in the rate of change of mean IOP over time between groups ($p < 0.001$). In the control group, day 0 IOP did not significantly differ from IOP measured at days 7, 21, and 42, whereas in the washout group, IOPs measured on these days were all significantly greater than day 0 IOP ($p < 0.002$). At each time point other than day 0, mean IOPs of the washout group were significantly greater than those of the control group ($p < 0.002$), with the magnitude of the difference increasing over time.

Despite the differences in IOP changes between groups, the majority of patients (75.3%) maintained IOPs < 21 mm Hg at 6 weeks post-washout, thus supporting the notion that prolonged PGA use may have sustained effects after discontinuation. This finding invites further questions. What is the mechanism responsible for this effect? Long-term PGA use may impact ocular structures, possibly remodeling the extracellular matrix and relaxing ciliary muscle bundles[3,10–12] or reducing central corneal thickness.[13] More basic science research is needed to investigate the definitive mechanisms at play. Questions also arise regarding how long the IOP-reducing effects last after discontinuation. Conflicting results have been reported, with some research showing no return to the pretreatment IOP baseline 3 weeks after PGA washout,[14] other research showing a return to pretreatment IOP after 4 weeks,[15] and the current study reporting that the majority did not return to pretreatment baselines at 6 weeks. Future studies should determine both the duration of post-washout effects and define what constitutes "long-term" PGA use that would confer such benefits.

There are clinical implications to the findings reported in this issue by Lim et al. The lingering effects of chronic PGA use after discontinuation should be accounted for when investigating the efficacy of secondary interventions or when crossing over to alternative glaucoma treatments. This aims to avoid overestimating the effects of the therapies being investigated. For this reason, the authors concluded that an optimal clinical protocol for PGA discontinuation is warranted.

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Visual outcomes and photic phenomena following bilateral extended depth of focus intraocular lens implants

Aishwarya Sundaram, PGY-4

Over the years, multifocal and extended depth of focus (EDF) intraocular lenses (IOLs) have been developed to provide patients with the opportunity for spectacle-free correction post-cataract surgery. While multifocal lenses offer sharp visual acuity at distinct foci with a drop in acuity between these points,[1] EDF IOLs provide a continuous range of good visual acuity between certain depths of focus.[2] Both types of lenses have been associated with photic phenomena, but multifocals have traditionally been associated with worse photic phenomenon.

In this issue, Lamba et al. report on a series of 87 patients who underwent bilateral EDF Symfony ZXR00 lens insertion over a 2.5-year period.[2] The authors collected data on binocular uncorrected and corrected logMAR visual acuity at a distance of 6 meters (UCDVA and CDVA, respectfully) and uncorrected near vision at 40 cm (UCNVA). In addition to visual acuity, the studies secondary outcomes focused on self-reported photic phenomenon, including glare, halo, and dysphotopsias. The authors also reported on postoperative complications, additional postoperative procedures, and performed a subgroup analysis of monovision patients. Highlights of the authors' findings include:

- **Visual acuity:** Three weeks after surgery, patients had a mean UCDVA of 0.16 (SD: 0.14) and a mean UCNVA of 0.14 (SD: 0.11).
- **Photic phenomenon:** Some form of photic phenomenon was reported by 18.4% of patients, with halos being the most reported phenomenon.
- **Additional postoperative procedures:** Postoperatively, one (1.1%) patient underwent photorefractive keratectomy (2.3%) and two patients underwent limbal relaxing incisions (LRI) for residual astigmatism.

- **Monovision subgroup analysis:** The subgroup analysis did not reveal any significant differences in visual outcomes or photic phenomenon.

A recent systematic review and meta-analysis reported on a total of 1336 eyes that had Tecnis Symfony IOLs implanted.[3] The authors showed that EDF IOLs were comparable with trifocal and monofocal lenses for distance visual acuity, and for near visual acuity and intermediate visual acuity, they found that EDFs were better than monofocal lenses—however, they also found that EDFs were comparable to trifocals for intermediate visual acuity and worse than trifocals for near visual acuity. Furthermore, the review found that EDF lenses offered better contrast sensitivity than trifocals in scotopic conditions and that both trifocal and EDF lenses were generally associated with similar rates of photic phenomenon.

Clinical practice point: When counselling a patient that desires both near and distance correction, EDF IOLs appear to be a good option. Comparing trifocals with EDFs in the broader literature, EDFs provide reasonable distance and near visual acuity with better contrast sensitivity. However, trifocals provide better near visual acuity at the expense of reduced contrast sensitivity. Regarding photic phenomenon, both lenses have similar rates of occurrence, but it is unclear if the severity of the disturbances are different between the two lenses. Monofocal lenses provide the best contrast sensitivity and minimal photic phenomenon for the patient that is only interested in optimal distance vision correction. With an increasing number of lens options in the market, the need for careful patient education on the benefits and drawbacks of the various IOLs is paramount to ensuring patient satisfaction.

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The problem with pressures

Laura Donaldson, PGY-5

For a trainee thinking about how to optimize clinic flow in their own practice, the question inevitably arises: should all patients receive dilating drops prior to being seen? The time saved must be balanced against potential issues, including inability to check for a relative afferent pupillary defect, potentially inaccurate intraocular pressure (IOP) measurement, and the possibility of precipitating angle closure in high-risk patients. There is also the problem of when IOP should be measured and by whom—the physician or a technician. Goldmann applanation tonometry (GAT) is considered the gold standard, but it requires application of anaesthetic drops, usually along with fluorescein dye, and may be inaccurate or impossible in patients with corneal pathology. Many physicians prefer not to delegate the task of GAT, and will have a technician use an alternate method, commonly a hand-held Tonopen. The Diaton transpalpebral tonometer (DAT) and rebound tonometers such as the ICare are other options, both of which have the advantage of not requiring topical anaesthetic drops.

In this issue, Qian and colleagues look at the effect of mydriatic drops on IOP measured with the DAT and GAT.[1] Sixty-seven adult patients attending a general ophthalmology clinic were included and had pressures in both eyes measured before and after pupillary dilation using a combination of phenylephrine and tropicamide. Mean predilation IOPs for the right and left eyes, respectively, were 16.7 mm Hg and 16.0 mm Hg using GAT and 11.9 mm Hg and 12.3 mm Hg using DAT. Postdilation, values changed by a mean of -1.05 mm Hg and -0.65 mm Hg for GAT and -0.13 mm Hg and +0.06 mm Hg for DAT. These data show that overall, much lower pressures were obtained with DAT; the lowest IOP recorded with GAT was 9 mm Hg versus a low of 5 mm Hg with DAT. As pressures changed in both directions, the mean IOP change was quite small. However, both methods showed a large amount of variability in IOP post-dilation, as much as -6 mm Hg or +5 mm Hg using GAT and -8 mm Hg to +7 mm Hg using DAT.

These results agreed with a previous study done by members of this group, which showed that 35% of patients had a change in IOP of 2 mm Hg or more post-dilation using GAT.[2] Taken together, these results support a recommendation that IOP measurements be taken prior to dilation. For glaucoma patients, where a difference of even 1−2 mm Hg may impact treatment decisions, this would be particularly important. Though this study specifically excluded patients with glaucoma, dilation may have an even greater effect in this population.[3] GAT showed less variability than DAT and poor correlation was found between the two methods in the current study and in others,[4] and as such, GAT has yet to be dethroned as the gold standard. When accuracy is most needed, other tonometry methods should be reserved for scenarios where GAT is not possible, such as in young children and non-cooperative patients[5] or in the presence of a keratoprosthesis.

As the authors state, when it comes to the best alternative to GAT, "the search is still on"!

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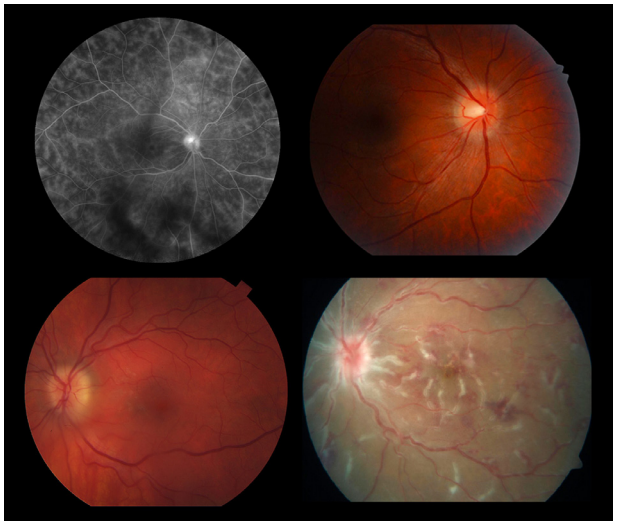

Resurgence of ocular syphilis in British Columbia: a resident's perspective

Gareth D. Mercer, PGY-3

Syphilis continues to be a disease of global significance. Over the last decade, the incidence of syphilis has rebounded in high-income countries, purportedly due to concentrated epidemics among vulnerable populations, including men who have sex with men, sex workers, and transgender women.[1] In low-and-middle income countries, the infection is endemic in the general population.[1] Ocular syphilis may develop during any stage of the infection and may involve any ocular structure.[2]

In the current issue, Eslami et al. present the findings of their population-based, retrospective review of ocular syphilis cases in British Columbia from 2013−2016.[3] The annual incidence of ocular syphilis in their study was around 3 per 1 million, or 1.1% of reported syphilis cases. Of this group, 60% were men who reported having sex with men and 51% were HIV co-infected. About half had secondary syphilis and the remainder had latent disease (15% late latent). In addition, 78% manifested either panuveitis or posterior uveitis. All cases were appropriately treated for neurosyphilis and visual outcomes were generally good, with 76% having final visual acuities $\geq$ 20/40. However, 13% of patients were lost to follow-up after their first visit and 3 patients with a final visual acuity of $<$ 20/200 were followed for 2 weeks or less.

From a resident perspective, there are 3 essential learning points from this study:

1. Syphilis and HIV are synergistic pathogens. Syphilis ulcers may aid in the acquisition of HIV, and HIV infection appears to modify the natural history of syphilis, potentiating neurosyphilis.[2] Reported rates of co-infection are between 20−70%.[2] Ocular syphilis occurs in as many as 10% of HIV-infected people.[2] It is essential that patients diagnosed with ocular syphilis are also screened for HIV. Furthermore, ophthalmologists ought to be aware that in Canada we have an obligation to report newly identified syphilis cases to our provincial or territorial public health agencies.[4]
2. The diagnosis of ocular syphilis may be delayed by a lack of awareness of the resurgence of this infection, and because of the highly variable clinical presentation. Delayed diagnosis may lead to irreversible optic nerve

and retinal damage and is associated with poorer visual prognosis.[5] It is essential to have a high index of suspicion and to consider syphilis screening for all uveitis patients. Although relatively rare, two particular forms of posterior uveitis that have high positive predictive values for syphilis infection are: a) confluent inner retinitis associated with multiple pre-retinal precipitates, and b) acute syphilitic posterior placoid chorioretinitis.[6]

3. Ocular syphilis is regarded as a subtype of neurosyphilis. As per Canadian guidelines, patients with suspected or confirmed ocular syphilis require evaluation for neurosyphilis, including cerebrospinal fluid analysis for cell count and differential, protein and VDRL and/or fluorescent treponemal antibody absorbed assay.[4] Intramuscular Benzathine penicillin G, the standard treatment for other forms of syphilis, is inadequate for neurosyphilis, for which the recommended treatment is intravenous aqueous Penicillin G for 10-14 days.[4] Posttreatment, sequential non-treponemal serologic testing is recommended to assess for treatment success and patients with CSF abnormalities require repeat CSF testing until normalization.[4]

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Colour discrimination and stereoacuity: a commentary

Matthew D. Benson, PGY-4

Stereopsis is a product of excellent visual acuity and ocular alignment and it creates a perception of depth when an object is viewed binocularly. With rudimentary stereopsis evident as early as 3 months of age, the visual system undergoes rapid development with improvement in stereopsis occurring over the first few years of life.[1] Stereoacuity, a quantitative measure of stereopsis, is a parameter that is especially relevant in pediatric populations, where it can serve as an indicator of binocular control in patients with strabismus. Both contour-based (Titmus test) and random dot-based (TNO and Lang test) techniques exist for evaluating stereoacuity in the clinic.[2] Given the importance of stereoacuity as a measure of visual function, it is critical to examine the factors that can influence it, such as colour discrimination.

In this issue, Koctekin et al. examined the relationship between measures of colour discrimination and stereoacuity.[3] While prior studies have suggested that stereoacuity is impaired in patients with color deficiencies, the current study compared patients with congenital colour vision deficiency (CCVD) to healthy participants in an effort to more generally assess the relationship between color vision and stereoacuity.[4,5] The authors compared 27 males with anomalous trichromacy (20 deutan and 7 protan males) to 26 males without CCVD by analyzing responses on the Farnsworth Munsell 100 (FM100) hue test and the TNO and Titmus stereo tests.[3] Significantly reduced stereoacuity, measured on both stereo tests, occurred in the CCVD group compared with the healthy controls, supporting previous studies.[4,5] This finding is clinically relevant as it highlights, for example, the importance of determining whether a patient with strabismus has CCVD as color deficiency might affect the level of stereoacuity a patient could achieve.

A unique finding in this study occurred in healthy controls undergoing the TNO stereo test and FM100 hue test. When results from these tests were correlated, higher blue-yellow error scores (indicating poorer blue-yellow colour discrimination) on the FM100 were significantly associated with poorer performance on the TNO stereo test. Interestingly, this relationship was not found in patients with CCVD. The authors did not, however, comment on whether there was a correlation between performance on the Titmus stereo test and FM100 hue test in patients with normal colour vision.

Although the precise mechanism for developing stereopsis is not fully understood, neurons involved in processing paired images of random-dot patterns have been identified in the visual cortex.[6] In this issue, Koctekin et al. speculate that the finding of an association between blue-yellow color discrimination and stereoacuity may implicate an overlapping role of neurons involved in blue-yellow color processing and stereopsis. Given that tritan defects are encoded on chromosome 7 and are therefore not sex-linked, it would be interesting to assess whether the same relationship between blue-yellow color discrimination and TNO stereoacuity is present in females.

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