Resident Perspectives: Ocular hypertension following periorcular and intraocular steroid administration

Increased intraocular pressure (IOP) is a well-established potential complicating factor of steroid use. Definitions for what constitutes a steroid response vary and may include an IOP increase by 5mmHg from baseline, an IOP increase above 21 or 24mmHg, or an increase by 10mmHg from baseline. Armaly and Becker (1965) described a moderate IOP increase (6 to 15mmHg) in 33% of patients on topical steroids and a high IOP increase (>15mmHg) in 4-6% of patients on topical steroid therapy. The onset of increased IOP can range from hours or days to weeks or months following steroid use and depends on many factors including the strength of the steroid and route of administration. Risk factors for a steroid response include a personal or family history of glaucoma, high myopia, type 1 diabetes mellitus, and connective tissue disease. A steroid response could lead to steroid-induced glaucoma, a form of secondary open-angle glaucoma, due to increased resistance to aqueous outflow at the level of the trabecular meshwork. While several studies have evaluated the IOP responses following periorcular and intraocular steroid use, there has not been a study that has directly compared IOP responses for all indications based on the route of steroid administration.

In this issue, Kuley and colleagues compare the incidence of ocular hypertension, defined as IOP >24mmHg, in a retrospective series of patients receiving either 40mg of sub-Tenon triamcinolone (STT), 0.7mg dexamethasone implant (DEX), or 2mg of intravitreal triamcinolone (IVT) for any indication. Patients were excluded if they had received any form of steroid within 3 months of the initial injection. The authors reported that ocular hypertension occurred in 17.7% of the STT group, 15.6% of the DEX group, and 12.8% of the IVT group, and that these incidences were not significantly different from each other. Interestingly, the occurrence of ocular hypertension was the same in all treatment groups regardless of whether patients had a history of glaucoma or not. In addition, the route of steroid administration did not affect the peak IOP reached, the time to develop elevated IOP, or the medical or surgical management of the elevated IOP.

This article has several strengths, including incorporating a modest number of patients in each treatment group and evaluating outcomes over a long follow-up period. The latter point is particularly important since IOP elevation may occur many months and even years after the initial steroid exposure. One of the limitations in the study, however, is that the authors excluded patients who had less than 3 months of follow-up after injection. This is problematic since the authors tabulated ocular hypertension in the remaining participants and reported incidences of IOP rise within 3 months of injection. In addition, the authors excluded patients who received steroids other than STT, DEX, or IVT during the follow-up period. While this may be necessary to isolate IOP changes specifically related to the periorcular or intraocular steroid use, it may also result in a lower incidence of steroid response compared to what truly exists. Finally, it may have been helpful to compare IOPs between the three groups prior to injection since the risk of steroid response has been shown to be affected by baseline IOP.

In summary, Kuley and colleagues evaluated the effect of periorcular and intravitreal steroid use on IOP in a group of patients with multiple ocular diseases requiring steroids. As mentioned in the article, this study is the first to make this comparison for all indications for steroid use. While the incidence and timing of steroid response seem similar between patients receiving periorcular and intravitreal steroids, differences in baseline characteristics (in particular, indications for treatment) make it difficult to conclude with certainty that the steroid responses from these routes of administration are, in fact, the same.

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Resident Perspective: Noninfectious endophthalmitis following intravitreal triamcinolone acetonide

Triamcinolone acetonide is a synthetic corticosteroid effective, either as an intravitreal or periocular injection, in the treatment of cystoid macular edema (CME) from various uveitic and retinovascular diseases. Although anti-VEGF agents have largely supplanted triamcinolone as first-line therapy for CME in diabetic retinopathy and retinal vein occlusion, it is still commonly used in refractory cases or as combination therapy with anti-VEGF agents. Vision-threatening potential complications of intravitreal triamcinolone therapy include cataract, glaucoma and endophthalmitis. In this issue, Mason and colleagues review the literature on non-infectious endophthalmitis following intravitreal triamcinolone acetonide (IVTA). Their article clearly lays out the differential diagnosis for this entity, which includes infectious endophthalmitis, and pseudoendophthalmitis. It is critical to be cognizant of this differential diagnosis given significant treatment and prognostic differences between the entities. While pseudoendophthalmitis is caused by precipitation of triamcinolone crystals in the anterior chamber, and is not associated with typical symptoms of inflammation, both infectious and non-infectious endophthalmitis entail true anterior and posterior segment inflammation. In contrast to acute infectious endophthalmitis, non-infectious endophthalmitis may present with milder degrees of conjunctival injection and pain and has a self-limiting course, generally lasting 1-3 weeks. Although incompletely understood, proposed mechanisms for non-infectious endophthalmitis following IVTA include reactions to excipients and/or preservatives, and mechanical and rheologic stress caused by small particles. The incidence rate in the reviewed studies was between 0.1-7.3%, meaning that it may be more common than infectious endophthalmitis, which has an estimated incidence of 0.9% following IVTA.

By definition, microbial cultures are negative in cases of non-infectious endophthalmitis. However, as Mason and colleagues point out, cultures from anterior chamber and vitreous biopsy are often negative even in cases of infectious endophthalmitis. In any event, as culture results are generally unavailable at presentation, initial treatment decisions must be based on the clinical impression. While one may reasonably distinguish non-infectious from infectious causes of endophthalmitis based on presenting signs and symptoms alone, the present review demonstrates that antimicrobial agents will, regardless, be administered as a precaution in most cases. One area for future study is the extent to which PCR-based methods could avert unnecessary antibiotic treatment in cases of non-infectious endophthalmitis.

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Versatility of the choroid: effect of vitamin D on choroidal thickness

From grade school to medical school, we have learned about the spectrum of health diseases arising from vitamin D deficiency including osteoporosis, atherosclerosis and kidney diseases among many others. Recent literatures have also attributed vitamin D deficiency to ocular diseases such as age-related macular degeneration, glaucoma and dry eyes. A high prevalence of vitamin D insufficiency in the Canadian population, especially among women, warrants a closer look at how vitamin D supplementation can impact the visual system.

In this month’s issue, Öncil and colleagues demonstrated that subfoveal, nasal and temporal choroidal thickness was significantly lower in patients with low serum vitamin D levels. However, after vitamin D replacement, a significant increase in choroidal thickness was found compared to baseline measurements in the deficient group. The authors compared 65 vitamin D-deficient patients, similar in age and gender, to 60 healthy control patients. In both groups, the choroidal thickness in the subfoveal, nasal and temporal regions at 1.5 μm and 500 μm from the fovea was measured with enhanced depth imaging optical coherence tomography (EDOCT). Vitamin D deprived patients were treated with 300,000 IU cholecalciferol over 3 months and re-evaluated with OCT. There was no difference between central macular thickness between the treatment and control groups, but a positive correlation was noted between serum vitamin D values and subfoveal, temporal, and nasal choroidal thickness.

At the cellular level, vitamin D’s reversible effect on the choroid demonstrates a protective role in ocular health. Vitamin D receptors are expressed in isolated retinal vascular endothelial cells, pericytes as well as cells of the ganglion layer, inner nuclear layer, retinal photo receptor, and pigment epithelium layers. Supportive evidence have demonstrated that vitamin D is able to reduce inflammatory mediators, enhance barrier function, and induce cell death of tumor cells. A possible role of vitamin D acting in the choroid via a paracrine/autocrine pathway has also been suggested by other researchers. Through immunohistochemical staining, the presence of vitamin D receptors in retinal and choroidal endothelial cells were detected. The expression of enzymes involved in the metabolism of vitamin D (CYP27B1 and CYP24A1) was then confirmed by molecular biology. Correlating to the changes in serum vitamin D levels, the authors of this article showed a reversible change in subfoveal choroidal thickness, at 1.5 μm from the avascular fovea. Since the choroid is the only source of metabolic exchange for the avascular fovea, a change in perfoveal choroidal thickness, presence of these regulatory enzymes and vitamin D receptors, as shown in literature, suggest a direct effect of vitamin D on the choroidal vasculature.

It has been also stated that lower vitamin D levels are associated with reduced macular thickness among older patients, even in those without maculopathy. However, central macular thickness was not different between the two patient groups in this study, possibly due to the younger age of the study cohort. The authors provide evidence that the acute changes associated with vitamin D deficiency, including endothelial dysfunction and resultant choroidal thinning, is reversible with replacement of vitamin D. To date, few literatures have been published about the direct effect of vitamin D replacement on ocular health. Öncil and colleague’s paper sheds some light on acute changes within the choroidal plexus and suggests that early choroidal thickness may be reversible. Future in vivo studies are warranted to investigate the protective effects of vitamin D in pachychoroid and degenerative chorioretinal diseases.

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Resident Perspective: 3D analysis of choroidal vessels in eyes with Vogt-Koyanagi-Harada

Vogt-Koyanagi-Harada (VKH) disease is a systemic autoimmune disease affecting pigmented tissues. In the eye, it presents as a bilateral granulomatous panuveitis with other associated ocular manifestations such as serous retinal detachments, cilio-choroidal detachments, and importantly, choroidal thickening. Multimodal imaging techniques, including indocyanine green angiography (IGCA), fluorescein angiography (FA), and optical coherence tomography (OCT), are useful in the diagnosis and monitoring of treatment response in VKH. The choroid is the primary focus of inflammation in VKH and various reports have demonstrated changes on OCT in choroidal thickness after corticosteroid therapy. Thus, choroidal thickness can act as a marker of disease status, and characterization and quantification of choroidal changes can provide more detailed information about treatment response.

In this issue, Sugitani and colleagues discuss their 3-dimensional analysis of choroidal vessels in VKH before and after treatment using binarized swept-source OCT (SS-OCT) and ultrawide-field ICGA (UWIFICGA) images. This retrospective, observational case series analyzed 7 eyes with VKH and 8 control eyes. VKH eyes were treated with IV prednisolone within 15 days after disease onset, followed by a tapering dose of oral prednisone. Using ImageJ software, the authors used a binarization technique using UWIFICGA and ultrawide-field FA (UWFFA) images to determine choroidal vessel density in controls and VKH eyes in the acute and convalescent stages. A binarization technique using SS-OCT images was also used to quantify luminal versus stromal areas of the choroid within and among groups.

Expectedly, mean logMAR best corrected visual acuity (BCVA) significantly improved and mean subfoveal choroidal thickness significantly decreased after treatment. When comparing choroidal parameters, 2D choroidal vessel density in the posterior and midperipheral areas of VKH eyes in the acute stages was lower than that of controls (p < 0.01) but recovered to similar levels to the control eyes in the convalescent stage. Vertical analysis of choroidal vessels revealed that in the acute stages, the choroidal stroma was significantly expanded and choroidal lumina significantly constricted compared to the convalescent stage. This can be explained histopathologically, in which eyes with VKH demonstrate lymphocytic infiltration in the choroidal stroma, resulting in stromal swelling. Combining these vessel density analyses together provides a wide 3D analysis of choroidal vessels that is able to quantify a larger area when compared to OCTA analysis. Since OCT, IGA, and FA are often part of the work-up for suspected VKH, choroidal vessel density analysis using the binarization technique outlined by Sugitani and colleagues could be readily available clinically and used for patient monitoring and treatment guidance. Future work could investigate the relationship of vessel density and its changes after treatment with improvement in clinical parameters, such as BCVA. Its utility as a prognostic factor could also be explored to determine the expected degree of treatment response for individual patients. Furthermore, once the binarization algorithm has been shown to be accurate and reproducible, its application in other chorioretinal diseases, such as diabetic retinopathy and age-related macular degeneration, can be investigated. This would allow for a deeper understanding of the pathophysiology of various diseases, and the subsequent clinical translation of this information.

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