Topical timolol for the treatment of conjunctival pyogenic granulomas: Outcomes and effect on intraocular pressure

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Purpose: To report the clinical outcomes of 0.5% timolol maleate eye drops for the treatment of conjunctival pyogenic granuloma (PG) and its effect on intraocular pressure (IOP). Methods: In this retrospective study, consecutive patients with conjunctival pyogenic granuloma between January 2019 and September 2019 were prescribed 0.5% timolol maleate eye drops twice a day and followed up for 8 weeks. IOPs were measured before treatment, while on treatment and 6 weeks after treatment. Results: A total of 12 patients with conjunctival PGs were treated with 0.5% timolol maleate eye drops. Patients ranged from 7 to 72 years with a mean age of 31.1 years. Eleven (11/12; 91.6%) patients had complete resolution of pyogenic granulomas after a mean duration of treatment of 4.4 weeks (range: 3–6 weeks). One patient had a persistent PG, which showed sub-optimal resolution at 6 weeks of treatment and was surgically excised. The mean IOP of the affected eye at presentation was 15.1 mm Hg (range: 10 to 20 mm Hg; SD: ±2.9 mm Hg). One week after initiating therapy, the mean IOP was 12.1 mm Hg (range: 8–16 mm Hg; SD: ±4.4 mm Hg). The mean reduction IOP compared to the baseline IOP was statistically significant (p = 0.02). No adverse events were noted in any of the patients. Conclusion: Topical timolol is effective in the treatment of conjunctival pyogenic granulomas with no major side effects. There is a significant reduction in IOP while on treatment which is reversible and returns to baseline following completion of therapy.

Key words: Beta-blockers, chalazion, eyelid, lobulated capillary hemangioma, tumor

Pyogenic granuloma (PG) is a benign condition commonly encountered in clinical practice. It is an acquired vascular lesion commonly seen on the skin and mucosal surfaces. In the eye, PGs, also known as lobular capillary hemangiomas, are typically seen on the palpebral or bulbar conjunctiva following any form of inflammatory insults such as surgery, burst chalazion, ill-fitting ocular prosthesis, and trauma. They may bleed spontaneously, which can be very alarming for patients. The other common clinical complaints include foreign body sensation, irritation, discharge, unsightly mass, and rarely pain. There are many treatment options for cutaneous PG including topical steroids, imiquimod, silver nitrate, cryotherapy, electrocautery, laser ablation, or surgical excision.[¹]

The most commonly preferred treatment for ocular surface PGs is topical steroid therapy (ref). Topical steroids usually are initiated at a frequency of four to six times a day and then tapered for weeks. In case topical steroid therapy does not lead to resolution of the PG, surgical excision is the next preferred technique which apart from being an invasive option, also requires general anesthesia in children. Topical steroids are known to cause a rise in intraocular pressure (IOP): it has been noted that with extended use, topical steroids can cause ocular hypertension, with a 6 to 15 mm Hg rise in IOP after 4 to 6 weeks of use in 30% of healthy patients.[²] Furthermore, diagnosing and treating this rise in IOP is an additional challenge in children. Therefore, to avoid the inherent risks of sustained topical steroid therapy, topical timolol has been thought to be a viable option for the treatment of PGs. Recent publications suggest that topical timolol, a non-selective beta-blocker is an effective, non-invasive treatment option for cutaneous PGs.[³–⁵] With regard to ocular PGs, there have been three previous publications that have reported the outcomes of topical timolol for the treatment of PGs.[⁶,⁷] This manuscript represents the first such report on the use of topical timolol for ophthalmic PGs in the Indian population.

Methods

The charts of 12 consecutive patients with conjunctival PG seen by the senior author were reviewed. All patients were prescribed 0.5% timolol maleate twice daily with punctal occlusion. The data analyzed included the following parameters: age, sex, duration of symptoms, location of PG, previous treatment received, duration of treatment, outcome, IOP at first pre-treatment visit, IOP after at least one week after treatment initiation, and IOP at final visit which was at

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least 6 weeks after treatment cessation. All patients underwent comprehensive ophthalmologic examination including visual acuity, IOP by applanation tonometry, and fundus evaluation. Complete resolution of the granuloma at 6 weeks was considered as treatment success. If after 6 weeks of topical therapy, incomplete resolution of the lesion was not observed, of it was evident that any further treatment would not lead to any improvement – treatment was stopped, and surgical excision was offered. Exclusion criteria included recurrent PG at presentation/follow-up, previous diagnosis of glaucoma or ocular hypertension, any concurrent anti-glaucoma medication and follow up of <8 weeks. Pregnant women, patients with a history of bronchial asthma were also excluded.

Regarding IOP measurement, calibration of the tonometer was verified according to the manufacturer’s instructions, the tip was cleaned before each measurement was made and topical proparacaine 0.5% was instilled before each measurement. All measurements were taken between 1100 to 1500 hours in all patients and all patients were photographed at every visit after obtaining written consent. Institutional review board approval was obtained, and the study was conducted in accordance with the Declaration of Helsinki.

Results

Study participants

Seven (7/12; 58.3%) patients were males. The age of the patients ranged from 7 years to 72 years with a mean age of 31.1 years [Table 1]. In 7 patients, the right eye was affected; the cause of the PG was attributable to trauma (after ruling out the presence of any foreign body) in 2 (16.7%) patients; chalazion in 9 (75%) patients and one (8.3%) patient had undergone a squint surgery 6 weeks prior to presentation. The mean duration of symptoms prior to presentation was 4.7 weeks (range: 2 to 12 weeks). Morphologically 11 (91.6%) of the lesions were sessile and only one patient had a pedunculated mass. Four (33.3%) patients had previously received tapering topical steroids with minimal improvement noted prior to presentation.

Outcomes

Eleven (91.6%) patients had complete resolution [Figs. 1-3] of the PGs after a mean duration of treatment of 4.4 weeks (range: 3-6 weeks). Of the four patients who had received previous topical steroids, one patient had a persistent PG, which showed suboptimal resolution at 6 weeks of treatment and it was decided by the senior author to offer surgical excision [Fig. 4]. The mass was excised, and the histopathological examination was consistent with a PG. The mean duration of treatment that resulted in total resolution of the PG in those who had not received any previous steroids was significantly less at 3.8 weeks as opposed to 5.67 weeks the three patients who had received topical steroids therapy (p = 0.01).

Two patients aged 7 years and 9 years; in whom IOP measurement was not possible were excluded from the data analysis of changes in IOP. The mean IOP of the affected eye at presentation was 15.1 mm Hg (range: 10 to 20 mm Hg; SD: ±2.9 mm Hg). At one week after initiating therapy, the mean IOP was 12.1 mm Hg (range: 8 to 16 mm Hg; SD: ±2.4 mm Hg). The mean reduction IOP while on treatment, compared to the baseline IOP was statistically significant (p = 0.02). Subsequently, at the final follow-up, the mean IOP was 14.4 mm Hg (range: 10 to 18 mm Hg; SD: ±2.5 mm Hg) with the mean rise in IOP as compared to the IOP while on topical timolol was also significant (p = 0.04). The IOP measurements at the final follow-up were at least 6 weeks after the cessation of timolol, allowing for washout of the drug. Of the 11 patients who showed complete resolution after topical timolol, there were no recurrences with a mean follow-up of 5.3 months (range: 2 to 10 months). No local or systemic adverse events noted in any of the patients.

Discussion

PGs are also known as ‘lobular capillary hemangiommas’ and they represent benign, acquired, vascular tumors that are usually seen following an episode of inflammation such as surgery or trauma. PGs can occur at any age.[8] It is hypothesized that PGs occur secondary to local tissue hypoxia within the traumatized endothelial cells, which results in the expression of growth factors such as vascular endothelial growth factor and basic fibroblast growth factor, leading to aberrant healing and the eventual mass formation. It is plausible that conjunctival PG formation results from an angiogenic imbalance during wound healing.[9] In the eye, the location and appearance of PGs are recognizable and excisional biopsy is only performed when the lesion does not respond to conservative therapy in the form of topical steroids.

In addition to corticosteroids, the other treatment modalities used to treat ocular PGs include cryotherapy, electrocautery, topical antimetabolites, intralesional steroids, and plaque irradiation.[10‑11] However, for the ease of use and reasonably high success rates, topical corticosteroids have been the treatment of choice in most cases. Corticosteroids also reduce the size of PGs before surgical excision, thus minimizing the risk of further scar tissue. Espinoza and Lueder reported that for the treatment of conjunctival PGs, the use of topical corticosteroid gave a 90% success rate. The average duration of topical therapy in their cohort was approximately 30 days with some requiring up to 80 days of treatment.[12]

Topical steroid therapy, although convenient, is not free of side-effects. Steroid-induced ocular hypertension (SIOH) can lead to steroid-induced glaucoma (SIG), following prolonged use. Other potential side effects include opportunistic infections and cataract formation.[13] In general, 5% of the population reportedly exhibit high steroid responsiveness and 35% of the population have intermediate responsiveness to steroids.[14,15] This puts a reasonably large population at risk of developing raised IOPs following the administration of topical steroids. With sustained usage, topical steroids may induce ocular hypertension, with 30% of healthy patients experiencing a 6 to 15 mm Hg rise in IOP just after 4 to 6 weeks of use.[16] It has been observed that after the steroid therapy is discontinued, IOP usually normalizes within 1 to 4 weeks. However, in steroid-responsive patients, IOP elevation can develop within the first few weeks of steroid administration.[15] In children, in whom IOP measurement is not always possible, detection and management of raised IOP can be an issue.

Topical timolol has been used as an alternative to steroids for the treatment of PGs. The use of beta-blockers in the management of benign vascular lesions was first reported by Léauté-Labrèze et al.[17] This accidental discovery initiated the interest of clinicians in using beta-blockers in the treatment of
blockers cause vasoconstriction of capillaries supplying the hemangioma, inhibition of proangiogenic growth factors, and apoptosis of proliferating endothelial cells. Beta-blockers also target angiogenic factors such as vascular endothelial growth factor and basic fibroblast growth factor, which are required for the growth and maintenance of PGs.

Lubahn et al. first described the resolution of conjunctival sessile hemangioma with topical timolol. In their report, a 77-year-old African American woman developed an acquired sessile hemangioma of the conjunctiva of the right eye. She was followed for primary open-angle glaucoma, and the lesion was monitored for 12 months without change. Topical timolol-dorzolamide was then added to her glaucoma medication regimen twice daily. On follow-up examination 6 months later, the lesion had completely resolved. Following this, there have been two studies in which topical timolol (0.5%) eye drops have been used for the treatment of conjunctival PGs and have reported successful outcomes.

Oke et al. reported outcomes in 4 children who had conjunctival PGs. All children were only using topical timolol, 0.5%, twice daily and in all cases, complete resolution occurred within the treatment period with no recurrence for at least 3 months. There were no adverse effects from the timolol during follow-up. DeMaria et al. reported outcomes in 17 patients with ocular PGs: 88% (15/17) of the patients had complete lesion resolution with a mean treatment duration of approximately 3 weeks and no adverse events or recurrences with a mean follow-up of 9 months. However, in their series, two (12%) patients underwent lesion excision after 6 weeks of timolol failed to yield a resolution.

We report comparable success rates with the use of topical timolol with 91% of the patients responding to topical therapy. Demaria et al. mentioned that in their series, 76% of the lesions were sessile and the remaining 24% of the lesions being...
While topical timolol did produce a significant reduction in IOP (mm Hg) if topical timolol therapy fails. This study adds to the growing body of evidence suggesting that topical timolol should be the first line of therapy in ocular surface PGs.

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Conflicts of interest
There are no conflicts of interest.

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