Original Article

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: ±2.4 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.

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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.[1,6,7] 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 effected; 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 hemangiomas' 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.[9-11] 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

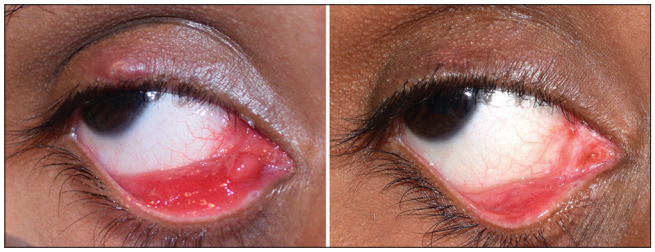

Figure 1: Case 5: A 23-year-old male who presented with a right lower lid sessile pyogenic granuloma (left) received topical timolol 0.5% for 4 weeks resulting in complete resolution (right)

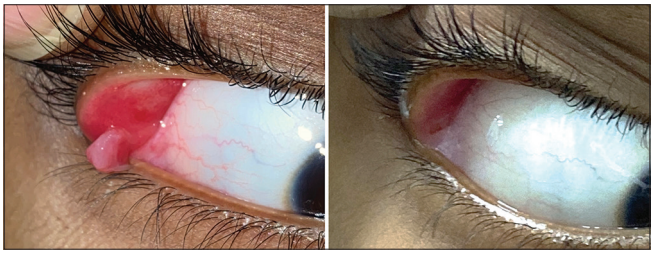

Figure 2: Case 2: A 9-year-old girl with a five-week history of a mass, which was noted after a chalazion had resolved (left) received timolol 0.5% for 3 weeks leading to a total resolution of the mass (right)

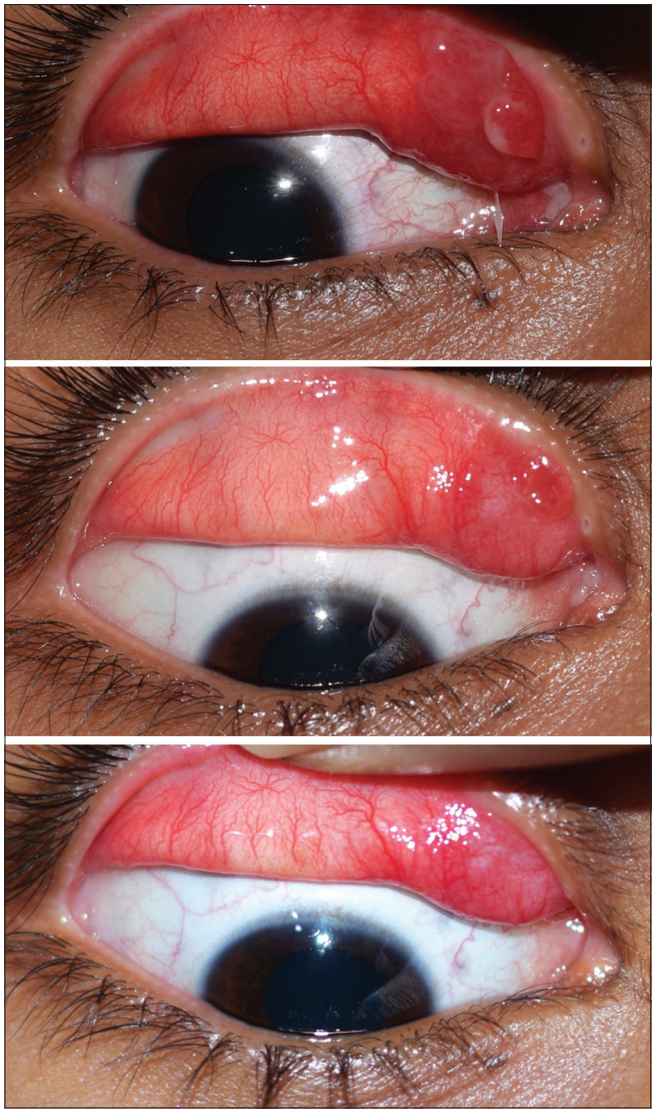

Figure 3: Case 7: An 18-year-old male with a large sessile pyogenic granuloma (top) received timolol eyedrops BD, resulting in partial resolution (middle) at 4 weeks and complete resolution at 6 weeks (bottom)

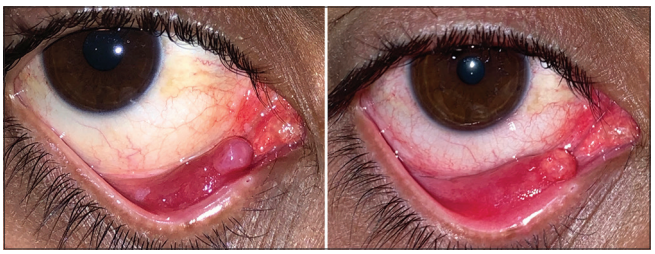

Figure 4: Case 11: A 24-year-old male with a persistent pyogenic granuloma (left), which did not resolve completely following 6 weeks of topical timolol (right) and was ultimately excised. Histopathology was consistent with a pyogenic granuloma

PGs as well. Throughout dermatology literature, multiple case reports have highlighted the anecdotal success of topical beta-blockers in the treatment of PGs on the skin.[4,18,19] The mechanism of action of beta-blockers in the treatment of hemangiomas is not completely well understood but it is hypothesized that beta-blockers cause vasoconstriction of capillaries supplying the hemangioma, inhibition of proangiogenic growth factors, and apoptosis of proliferating endothelial cells.[1] 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.[1,17]

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.[6] 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.[1,7]

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.[7] 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.[1]

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

Table 1: Summary of cases of pyogenic granuloma treated with topical timolol

Case	Age (years)	Sex	Eye	Location	Antecedent history	Duration of complaints (weeks)	Nature of PG	Previous treatment	Treatment duration	Outcome	IOP (mm Hg)			Follow up (months)
											Pre-treatment	On medication	Post treatment	
1	7	M	OS	PC	Trauma	2	Sessile	Nil	4	Resolved	NM	NM	NM	8
2	9	F	OD	PC	Chalazion	5	Sessile	Nil	3	Resolved	NM	NM	NM	2
3	34	M	OD	PC	Chalazion	4	Sessile	Nil	3	Resolved	18	15	17	9
4	55	F	OS	PC	Chalazion	4	Sessile	Nil	3	Resolved	17	13	17	10
5	23	M	OD	PC	Chalazion	2	Sessile	Nil	4	Resolved	16	13	15	3
6	72	F	OD	PC	Trauma	4	Pedunculated	Topical steroids	6	Resolved	20	16	18	4
7	18	M	OD	PC	Chalazion	7	Sessile	Nil	6	Resolved	14	11	13	2
8	24	M	OS	BC	Squint surgery	6	Sessile	Topical antibiotics, steroids	5	Resolved	10	8	10	3
9	41	F	OS	PC	Chalazion	12	Sessile	Topical steroids	6	Resolved	13	10	12	4
10	44	F	OS	PC	Chalazion	3	Sessile	Nil	4	Resolved	13	10	14	6
11	24	M	OD	PC	Chalazion	4	Sessile	Topical Steroids	6	Partially resolved - excised	16	13	15	2
12	22	M	OD	PC	Chalazion	4	Sessile	Nil	4	Resolved	14	12	13	8

M=Male, F=Female, OD=Right eye, OS=Left eye, PC=Palpebral conjunctiva, BC=Bulbar conjunctiva, PG=Pyogenic granuloma, IOP=Intraocular pressure, NM=Not measured

pedunculated. Only one patient each from the two groups underwent excision following poor response to timolol.[1] In our cohort, there was only one patient with a pedunculated lesion, which did not respond well to topical timolol and underwent excision. In our study, we observed that the mean duration of treatment leading to a total resolution of the PG in those who had not received any previous steroids was significantly less compared to those who had received topical steroids therapy. This was likely due to the larger size of the PGs in those patients who did not respond to steroid therapy.

With regard to the IOP reducing property of timolol, it was observed that timolol did lead to a significant reduction in IOP in all subjects. Timolol exerts its ocular hypotensive effect by reduction of aqueous humor production. This reduction in IOP ranges from 30-47% across many studies that included normal eyes.[19-23] While the IOP reduction is expected, it is equally important to explore if timolol could lead to any change in the blood circulation dynamics within the eye. Tamaki *et al*. reported that over a three weeks, twice daily topical timolol treatment had no deleterious effect on the optic nerve head tissue blood flow in the human eye.[24] In fact, over the years, animal studies, in vitro investigations, and clinical trials including normal volunteers, ocular hypertensive patients, primary open-angle glaucoma, and normal-tension glaucoma patients never showed data that was consistent enough to indicate a pernicious effect of timolol maleate on the retinal, choroidal, or optic nerve head circulations; thereby establishing the safety profile of timolol in healthy individuals.[25] While topical timolol did produce a significant but reversible reduction in IOP in all subjects in this study, no adverse reactions were reported.

Limitations of this study include the limited number of subjects, the absence of documentation of the size of the granulomas, and the lack of central corneal thickness measurements which could affect the IOP measurements. However, we believe there is sufficient evidence to offer topical timolol therapy over topical steroids as a safe option for patients with PGs. Surgical excision should be offered as an option only 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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