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Original Article

Improvement of Prostaglandin-Associated Periorbitopathy after Discontinuing Treatment

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Abstract

Objectives: To report that the periorbital changes induced by prostaglandin analogue (PGA) eye drops are partially reversible after discontinuing treatment.

Materials and Methods: Nine patients with prostaglandin-associated periorbitopathy seen in a referral oculoplastic practice were included in this study, eight with unilateral glaucoma and one with bilateral open-angle glaucoma. All of them had been treated with topical PGA for at least one year, before the treatment was discontinued for cosmetic reasons.

Results: In all cases, there were evident periocular differences between the treated eye and the fellow eye, consisting mainly of deepening of the upper eyelid sulcus and eyelid fat pad reduction. One year after discontinuing the PGA eye drops, improvement of these features was observed.

Conclusion: Clinicians and patients should be aware of the side effects of topical PGA therapy on periorbital tissues, and that these side effects can partially regress after discontinuation of the medication.

Keywords: Periorbitopathy, prostaglandin analogue, prostaglandin-associated periorbitopathy, periorbital changes

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Introduction

Prostaglandin analogues (PGAs) have been approved as a first-line drug treatment for glaucoma because of their intraocular pressure (IOP)-lowering effectiveness and their few systemic side effects.[1] However, PGAs cause side effects not only in the eye but also in its immediate surroundings.[2] In 2004, after more than a decade of the clinical use of topical PGAs, Peplinski and Smith[3] described deepening of the upper eyelid sulcus (DUES) in bimatoprost users, reporting it as a side effect of prostaglandin F2 alpha analogues. DUES was subsequently reported among users of other PGAs, including travoprost, tafluprost, isopropyl unoprostone, and latanoprost.[4,5,6,7,8,9,10,11] Since these observations were published, DUES became a frequently recognized cosmetic side effect of topical PGAs.

However, because similar changes have been observed in the lower eyelids, the term "prostaglandin-associated periorbitopathy" (PAP) was proposed as a general term for PGA side effects that occur around the eyelids.[12,13,14] PAP is now a recognized clinical entity that includes upper eyelid ptosis, DUES, involution of dermatochalasis, orbital fat atrophy, mild enophthalmos, flattening of the lower eyelid bags, inferior scleral show, and tight orbits.[10] These side effects usually appear several weeks to several years after initiating PGA therapy.[13]

There has been one report of irreversible DUES, even after the cessation of the eye drop treatment.[15] However, numerous other studies have described complete or partial improvement of PAP after treatment cessation or switching to latanoprost therapy.[3,4,5,16,17,18,19] The resolution time reported in these studies varied from a month to several years.

The purpose of the present study was to investigate the regression of PAP in patients who had been treated with topical PGAs for at least a year by comparing photographs obtained before and after suspension of PGA treatment.

Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local institutional review board. Written informed consent was obtained from all participants.

A retrospective chart review was performed on patients previously seen in a referral oculoplastic practice with eyelid and orbital changes attributed to the use of PGAs. All nine patients (10 eyes) included in this study had been under treatment with topical PGA eye drops for at least 1 year and developed PAP. Eight patients had unilateral glaucoma and one had bilateral glaucoma. They discontinued PGA therapy for cosmetic reasons. The same observer (J.M.A-L.) evaluated the periocular changes just before and 1 year after the patients discontinued PGA therapy. External and slit-lamp examinations were performed in all patients. To document the changes, photographs of the periocular region were obtained before and after PGA cessation. Dermatochalasis and lower eyelid steatoblepharon were evaluated according to the grading scheme reported by Shah et al.[14] We also assessed upper lid ptosis, levator muscle function, and inferior scleral show.

Results

The patients ranged in age from 58 to 93 years (mean 75.7 years); 5 were female and 4 were male. Eight patients received unilateral treatment, and one bilateral (patient 9). Two eyes had a previous history of cataract and vitrectomy surgery, two of cataract surgery, and one of cataract and ptosis surgery. Four eyes had no surgical history. Table 1 summarizes the dataset and results of this study. Figure 1 shows the patients' eyes after at least 1 year of PGA therapy and at 1 year after PGA therapy was discontinued.

Four eyes had pseudoexfoliative glaucoma, three open-angle glaucoma, two posttraumatic glaucoma, and one ocular hypertension. Bimatoprost 0.03% (Lumigan, Allergan Inc., Dublin, Ireland) was used in one eye, bimatoprost 0.03% plus timolol 0.5% (Timabak, Thea Pharma Inc., Barcelona, Spain) in four eyes, travoprost 0.004% (Travatan, Alcon AG, Geneva, Switzerland) in one eye, and travoprost 0.004% plus timolol 0.5% in four eyes, all once a day. Patients were under continued treatment for 12 to 60 months (mean 24 months). PGAs were discontinued in all eyes and replaced by brinzolamide 1% (Azopt, Alcon AG, Geneva, Switzerland) plus brimonidine 0.1% (Alphagan, Allergan Inc., Dublin, Ireland) twice a day in eight eyes, carteolol 1% (Arteoptic, Bausch & Lomb, Madrid, Spain) twice a day in one eye, and there was no replacement in one eye.

Changes in the periorbital region were evaluated using the grading scheme for assessment of dermatochalasis and steatoblepharon (inferior adnexal extraconal orbital fat herniation) published by Shah et al.[14]

After topical PGA therapy, DUES was observed in nine eyes (Figure 1: 1A, 3A, 4A, 5A, 6A, 7A, 8A, 9A), dermatochalasis involution in five eyes (Figure 1: 1A, 4A, 5A, 6A, 7A), and fat loss resulting in flattening of the lower eyelid pad in four eyes (Figure 1: 2A, 4A, 9A).

One year after discontinuing PGA therapy, DUES improved in eight patients (Figure 1: 1B, 3B, 4B, 5B, 6B, 7B, 8B, 9B), four eyes that had flattening of the lower eyelid bag recovered at least partially (Figure 1: 2B, 4B, 9B), and seven eyes showed an increase in upper eyelid dermatochalasis (Figure 1: 1B, 4B, 5B, 6B, 7B, 9B), creating a more symmetrical and cosmetically acceptable appearance. We observed no differences in upper lid ptosis, levator muscle function, or inferior scleral show.

Discussion

Historically, PGAs were regarded as having an acceptable side-effect profile, with the most common being increased iris pigmentation and eyelash lengthening.[20] The Ocular Hypertension Treatment Study found that 17% (65/380) of patients receiving PGAs presented changes in the iris, lashes, or skin.[21] The development of DUES and orbital fat atrophy may take from 1 month to 5 years.[15]

In 2004, Peplinski and Smith[3] described three patients on unilateral bimatoprost who developed ipsilateral reduction in dermatochalasis and DUES. These findings were later confirmed by Filippopoulos et al.,[16] who reported periorbital changes

Table 1. Characteristics of the patients

Patient	Eye	Prior surgery	Diagnosis	Treatment	PAP findings	Replacement	1 year post-PGA
1	Right	Cataract, vitrectomy	Posttraumatic glaucoma	Bima + Timo 15 mo.	Dermatochalasis involution DUES	Brinz + Brimo	Dermatochalasis increase DUES reduction
2	Left	None	Ocular hypertension	Travo 18 mo.	Lower fat pad loss	None	Lower fat pad recovered
3	Right	Cataract	Pseudoexfoliative glaucoma	Travo + Timo 18 mo.	DUES	Brinz + Brimo	DUES reduction
4	Right	Cataract, vitrectomy	Posttraumatic glaucoma	Travo + Timo 14 mo.	Dermatochalasis involution DUES lower fat pad loss	Brinz + Brimo	Dermatochalasis increase DUES reduction Lower fat pad recovered
5	Left	Cataract	Pseudoexfoliative glaucoma	Bimo 60 mo.	Dermatochalasis involution DUES	Carteolol	Dermatochalasis increase DUES reduction
6	Right	None	Open-angle glaucoma	Bimo + Timo 15 mo.	Dermatochalasis involution DUES	Brinz + Brimo	Dermatochalasis increase DUES reduction
7	Left	Cataract, Ptosis in both eyes	Pseudoexfoliative glaucoma	Bimo + Timo 12 mo.	Dermatochalasis involution DUES	Brinz + Brimo	Dermatochalasis increase DUES reduction
8	Right	None	Pseudoexfoliative glaucoma	Bimo + Timo 56 mo.	DUES	Brinz + Brimo	DUES reduction
9	Right	None	Open-angle glaucoma	Travo + Timo 16 mo.	DUES lower fat pad loss	Brinz + Brimo	Dermatochalasis increase DUES reduction Lower fat pad recovered
	Left	None	Open-angle glaucoma	Travo + Timo 16 mo.	DUES lower fat pad loss	Brinz + Brimo	Dermatochalasis Increase DUES reduction Lower fat pad recovered

Replacement: New treatment initiated after the periorbitopathy was observed, PAP: Prostaglandin-associated periorbitopathy, DUES: Deepening of the upper eyelid sulcus, Bima: Bimatoprost, Timo: Timolol, Travo: Travoprost, mo.: months of continued treatment, Brinz: Brinzolamide, Brimo: Brimonidine

associated with topical bimatoprost, including periorbital fat atrophy, DUES, relative enophthalmos, loss of lower eyelid fullness, and involution of dermatochalasis, compared with the untreated eye in a case series of five patients. They hypothesized that fat atrophy is the primary mechanism for these changes. Maruyama et al.[6] reported that 19% of patients treated with tafluprost, a new PGA introduced a few years ago, developed DUES within 90 days of starting treatment, yet only 17% of those affected had perceived any difference.

The analysis of orbital fat biopsies in PGA-treated patients showed reduction of adipocyte size with increased adipocyte density. Bimatoprost had the most pronounced effect on adipocyte density, followed by travoprost and latanoprost.[19] Systemic prostaglandins lead to changes in serum lipid levels, especially high-density lipoprotein levels, and are involved in adipogenesis.[22] Prostaglandin F2 alpha was found to be the most powerful preadipocyte differentiation inhibitor, suggesting that a prostanoid FP2 receptor mediates prostaglandin activity.[23]

Orbital and eyelid fat volume loss related to bimatoprost was confirmed on magnetic resonance imaging by Jayaprakasam and Ghazi-Nouri[24] in 2010. Since then, a retrospective study on patients undergoing unilateral PGA treatment found that bimatoprost induces more changes than travoprost or latanoprost.[7] Recent studies show that loss of periorbital fat is the most common feature, followed by involution of dermatochalasis, DUES, enophthalmos, and ptosis.[20] Our cohort of patients were either on bimatoprost or travoprost and developed some of these features to a greater or lesser degree. However, since our number of cases was small, we cannot conclude which PGA induces a higher degree of PAP.

The mechanism of ptosis in PGA users is unknown. One mechanism may involve an increase in matrix metalloproteinases that could lead to chemical dehiscence of the levator muscle from the superior tarsal plate.[14] We did not find evidence of marked upper lid ptosis induced by PAG treatment.

Although some of the eyes included in this study had a history of cataract, vitrectomy, or ptosis surgery, we believe this did not interfere with our observations because the surgeries were performed well before our first assessment of periocular features was made.

The periocular side effects of PGAs seem to be, at least in part, reversible. Some studies have shown that DUES and orbital fat pad loss were reversible from 1 to 24 months after discontinuation of bimatoprost.[3,15,16,17,25] Yam et al.[17] described a partial improvement in DUES after switching from bimatoprost to a combination of travoprost/timolol. Sakata et al.[26] found that DUES developed in 60% of Japanese patients within 6 months after switching from latanoprost to bimatoprost, but the DUES subsequently improved in 85% of affected patients within 2 months of switching back to latanoprost. Our findings largely

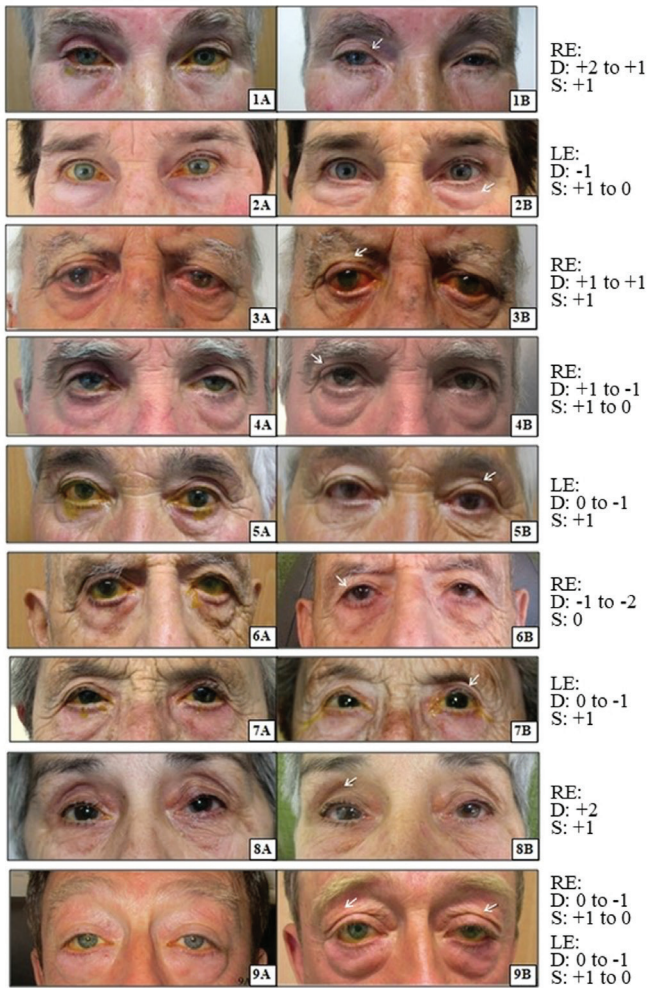

Figure 1. Changes before (A) and after (B) discontinuing PGA treatment. Changes at 1 year are marked with arrows in the B panels. 1A-B) Reduction of the deepening of the upper eyelid sulcus (DUES) and an increase in dermatochalasis in the right eye. 2A) Periorbital fat loss, especially in the lower eyelid; 2B) Inferior orbital fat is partially regained. 3A-B) Right DUES, partially resolved. 4A-B) Right DUES and lower lid orbital fat pad loss, both resolved. 5A-B) Left DUES and dermatochalasis, partially resolved. 6A) Right DUES and dermatochalasis involution; 6B) Increased dermatochalasis and reduced DUES. 7A-B) Left DUES partially improved and dermatochalasis increased. 8A-B) Right DUES, partially improved. 9A) Bilateral DUES and lower fat pad loss; 9B) DUES and orbital fat pad improved and dermatochalasis increased. D: Dermatochalasis score. S: Lower fat pad (steatoblepharon) score. S and D grading as reported by Shah et al.[14]

agree with the available reports in the literature. We observed improvement in most PAP features in our patients at 1 year after discontinuing PGAs.

Study Limitations

Our study is limited by its retrospective nature, the small number of patients, and the lack of a unified method to objectively record the periocular changes induced by PGAs. Another limitation of this study was that photographs of the patients before starting PGA therapy were not available. Nonetheless, the fellow untreated eye in eight of our nine cases was an excellent control for the natural aging process of the human periocular tissues.

Conclusion

In conclusion, patients and clinicians should be aware that PAP may appear with prolonged PGA use and can be especially apparent when PGAs are used unilaterally. The changes induced by PGAs can cause a significant asymmetry of the eyelid anatomy and cosmetic problems that could lead to poor drug compliance. It is possible, however, that the cosmetic effects of PGAs could lead to new treatment possibilities for orbital fat pad prolapse in the future. Further investigations to identify the biological mechanisms leading to these adverse effects would be necessary.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of Galicia (reg. nr. 2019/485).

Informed Consent: Patients signed informed consent.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: J.M.A-L., P.V.F., M.K.A., A.E.C., Concept: J.M.A-L., F.G., Dizayn: J.M.A-L., F.G., P.V.F., Data Collection or Processing: J.M.A-L., F.G., Analysis or Interpretation: J.M.A-L., F.G., Literature Search: J.M.A-L., F.G., P.V.F., Writing: J.M.A-L., F.G.

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References

1. Hollo G. The side effects of the prostaglandin analogues. Expert Opin Drug Saf 2007;6:45-52.
2. Alm A, Grierson I, Shields MB. Side effects associated with prostaglandin analog therapy. Surv Ophthalmol. 2008;53(Suppl 1):93-105.
3. Peplinski LS, Smith KA. Deepening of lid sulcus from topical bimatoprost therapy. Optom Vis Sci. 2004;81:574-577.
4. Yang HK, Park KH, Kim TW, Kim DM. Deepening of eyelid superior sulcus during topical travoprost treatment. Jpn J Ophthalmol. 2009;53:176-179.
5. Nakakura S, Tabuchi H, Kiuchi Y. Latanoprost therapy after sunken eyes caused by travoprost or bimatoprost. Optom Vis Sci. 2011;88:1140-1144.
6. Maruyama K, Shirato S, Tsuchisaka A. Incidence of deepening of the upper eyelid sulcus after topical use of travoprost ophthalmic solution in Japanese. J Glaucoma. 2014;23:160-163.
7. Kucukevcilioglu M, Bayer A, Uysal Y, Altinsoy HI. Prostaglandin associated periorbitopathy in patients using bimatoprost, latanoprost and travoprost. Clin Exp Ophthalmol. 2014;42:126-131.
8. Inoue K, Shiokawa M, Wakakura M, Tomita G. Deepening of the upper eyelid sulcus caused by 5 types of prostaglandin analogs. J Glaucoma. 2013;22:626-631.
9. Sakata R, Shirato S, Miyata K, Aihara M. Incidence of deepening of the upper eyelid sulcus on treatment with a tafluprost ophthalmic solution. Jpn J Ophthalmol. 2014;58:212--217.
10. Tan J, Berke S. Latanoprost-induced prostaglandin-associated periorbitopathy. Optom Vis Sci. 2013;90:245-247.
11. Yoshino T, Fukuchi T, Togano T, Seki M, Ikegaki H, Abe H. Eyelid and eyelash changes due to prostaglandin analog therapy in unilateral treatment cases. Jpn J Ophthalmol. 2013;57:172-178.

12. Nakakura S, Yamamoto M, Terao E, Nagatomi N, Matsuo N, Fujisawa Y, Fujio Y, Tabuchi H, Kiuchi Y. Prostaglandin-associated periorbitopathy in latanoprost users. Clin Ophthalmol. 2014;9:51-56.
13. Pasquale LR. Prostaglandin-associated periorbitopathy. Glaucoma Today. 2011;9:51-58.
14. Shah M, Lee G, Lefebvre DR, Kronberg B, Loomis S, Brauner SC, Turalba A, Rhee DJ, Freitag SK, Pasquale LR. A cross-sectional survey of the association between bilateral topical prostaglandin analogue use and ocular adnexal features. PLoS One. 2013;8:61638.
15. Aydin S, Işikligil I, Tekşen YA, Kir E. Recovery of orbital fat pad prolapsus and deepening of the lid sulcus from topical bimatoprost therapy: 2 case reports and review of the literature. Cutan Ocul Toxicol. 2010;29:212-216.
16. Filippopoulos T, Paula JS, Torun N, Hatton MP, Pasquale LR, Grosskreutz CL. Periorbital changes associated with topical bimatoprost. Ophthal Plast Reconstr Surg. 2008;24:302-307.
17. Yam JC, Yuen NS, Chan CW. Bilateral deepening of upper lid sulcus from topical Bimatoprost therapy. J Ocul Pharmacol Ther. 2009;25:471-472.
18. Aihara M, Shirato S, Sakata R. Incidence of deepening of the upper eyelid sulcus after switching from latanoprost to bimatoprost. Jpn J Ophthalmol. 2011;55:600-604.
19. Park J, Cho HK, Moon JI. Changes to upper eyelid orbital fat from use of topical bimatoprost, travoprost, and latanoprost. Jpn J Ophthalmol. 2011;55:22-27.
20. Custer PL, Kent Tl. Observations on prostaglandin orbitopathy. Ophthalmic Plast Reconstr Surg. 2016;32:102-105.
21. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK 2nd, Wilson MR, Gordon MO. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701-713.
22. Steinhäuser SL. Decreased high-density lipoprotein serum levels associated with topical bimatoprost therapy. Optometry. 2006;77:177-179.
23. Casimir DA, Miller CW, Ntambi JM. Preadipocyte differentiation blocked by prostaglandin stimulation of prostanoid FP2 receptor in murine 3T3-L1 cells. Differentiation. 1996;60:203-210.
24. Jayaprakasam A, Ghazi-Nouri S. Periorbital fat atrophy - an unfamiliar side effect of prostaglandin analogues. Orbit. 2010;29:357-359.
25. Tappeiner C, Perren B, Iliev ME, Frueh BE, Goldblum D. Orbital fat atrophy in glaucoma patients treated with topical bimatoprost--can bimatoprost cause enophthalmos? Klin Monatsbl Augenheilkd. 2008;225:443-445.
26. Sakata R, Shirato S, Miyata K, Aihara M. Recovery from deepening of the upper eyelid sulcus after switching from bimatoprost to latanoprost. Jpn J Ophthalmol. 2013;57:179-184.