

Bimatoprost-Induced Chemical Blepharoplasty

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ABSTRACT

We report significant changes in the appearance of the periorbital area, beyond eyelash enhancement, induced by the topical application of bimatoprost ophthalmic solution, 0.03% (Latisse[®], Allergan, Inc., Irvine, CA). To our knowledge, this is the first report in the dermatology or plastic surgery literature describing the rejuvenating effect and overall improvement in the appearance of the periorbital area resulting from applying Latisse to the upper eyelid margins. To date, reports in the literature discuss side-effects and potential complications of topical bimatoprost therapy causing a constellation of findings known as PAP (prostaglandin-associated periorbitopathy). While *periorbitopathy* implies pathology or a state of disease, we report changes that can be perceived as an improvement in the overall appearance of the periorbital area. We, therefore, propose a name change from PAP to PAPS – prostaglandin-associated *periorbital syndrome*. This better describes the beneficial, as well as the possible negative effects of topical bimatoprost. Although there is a risk for periorbital disfigurement, when used bilaterally, in properly selected candidates and titrated appropriately, bimatoprost can be beneficial. The striking improvement in the appearance of some individuals warrants further research into the potential use of topical bimatoprost to achieve a “chemical blepharoplasty.”

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INTRODUCTION

Bimatoprost is a prostamide – a synthetic analog of fatty acid amides – rather than a true prostaglandin, but it is typically referred to as a prostaglandin analog (PGA). PGAs have been used by ophthalmologists to treat glaucoma for many years. As with any drug, there are the intended therapeutic effects as well as unintended side effects and complications. Some of the side effects may be deleterious while others may eventuate in a new indication for the drug. Such was the case with bimatoprost. There was a serendipitous finding that glaucoma patients developed longer, darker eyelashes while instilling drops of bimatoprost into the eyes for the treatment of glaucoma.

Latisse[®] (topical bimatoprost solution, 0.03%; Allergan, Inc., Irvine, CA) was FDA-cleared for the purpose of eyelash enhancement in December, 2008; although not placed on the globe, as in the treatment of glaucoma, the cosmetic formulation of bimatoprost, applied topically to the upper eyelid ciliary margin, is exactly the same as Lumigan[®] (Allergan, Inc., Irvine, CA), the drug used in the treatment of glaucoma. With the appropriate application of the solution, the eyelashes become both longer and darker – an enhancement of the aesthetic appearance.

In addition to the lengthening and darkening of the eyelid cilia, other side effects associated with the ocular instillation of bimatoprost for the treatment of glaucoma have been noted by some ophthalmologists for over 10 years. The first case report was published in an optometry journal in 2004; three patients treated with unilateral bimatoprost developed

ipsilateral deepening of the upper eyelid sulcus and involution of dermatochalasis. These findings were reversed when the drops were discontinued.¹

The next publication of case reports was from the glaucoma service at the Massachusetts Eye and Ear Infirmary in 2008. They noted periorbital fat atrophy, deepening of the upper eyelid sulcus, relative enophthalmos, loss of lower eyelid fullness, and involution of dermatochalasis in five non-consecutive patients treated unilaterally for glaucoma with bimatoprost 0.03%. Imaging studies in two of the patients revealed the absence of primary orbital pathology and, like the 2004 report, there was partial reversal of these changes with discontinuance of the medication.² The authors postulated that PGA-mediated fat atrophy was responsible for the loss of preaponeurotic fat in the upper eyelid with resulting deepening of the upper eyelid sulcus and involution of dermatochalasis. Atrophy of the deeper periorbital fat resulted in the enophthalmos noted and diminished pseudoherniation of periorbital fat in the lower eyelids.

Subsequent publications began to emerge in the ophthalmologic literature with similar descriptions. Names such as “deep superior sulcus syndrome” or “DUES” – Deepening of the Upper Eyelid Sulcus – were used, but these names failed to recognize the entire constellation of findings that were noted with bimatoprost 0.03% used in treating glaucoma. It was not until 2011, however, in an ongoing collaboration between two glaucoma specialists, Dr. Stanley Berke and Dr. Louis Pasquale, that the name, “Prostaglandin-Associat-

FIGURE 1. 60-year-old woman treated for glaucoma of the left eye only with a PGA for 8 years. Note the following changes limited to the left periorbital area: mild ptosis of the upper eyelid, deepening of the upper eyelid sulcus, involution of dermatochalasis, periorbital fat atrophy, subtle inferior scleral show and tightness of the lower eyelid. Although she appears grossly disfigured due to the asymmetry of her eyes, one can appreciate that the left periorbital area appears rejuvenated due to a PGA-induced “chemical blepharoplasty.” (Photo courtesy of Dr. Stanley Berke)



ed Periorbitopathy” (PAP) was coined. PAP consists of eight clinical findings that were noted in patients treated with bimatoprost or the other PGAs for glaucoma.³⁻⁵ They were the following: 1.) upper eyelid ptosis, 2.) deepening of the upper eyelid sulcus, 3.) involution of dermatochalasis, 4.) periorbital fat atrophy, 5.) mild enophthalmos, 6.) inferior scleral show, 7.) increased prominence of eyelid vessels, and 8.) tight eyelids. What they did not include in their description of PAP was lengthening and darkening of the eyelashes, hyperpigmentation of the periorbital skin, or any changes in the color of the iris. According to Berke and Pasquale, the incidence of PAP is not uncommon. In fact, Berke states that it occurs in almost everyone on a PGA for glaucoma; one must be aware of it and know how to make the diagnosis⁶ (Figure 1).

During the post-marketing surveillance phase of Latisse, and because of the discovery and description of PAP, Allergan, the manufacturer of Latisse, modified the package insert. The following verbiage was added to reflect the changes noted in PAP: “periorbital and lid changes associated with a deepening of the upper eyelid sulcus.”

"Not everyone with ciliary hypotrichosis is a candidate for Latisse."

Nonetheless, prostaglandin-associated *periorbitopathy* refers to pathology or some state of disease. The findings in PAP are considered adverse side effects or complications of treatment. In some individuals, however, these findings may, in fact, be beneficial to the cosmetic appearance. Involution of derma-

tochalasis, deepening of the upper eyelid sulcus, periorbital fat atrophy, and tightening of the eyelid skin can simulate a blepharoplasty. Rather than view the constellation of findings described by Berke and Pasquale as PAP, we propose that, in properly selected individuals, used bilaterally and carefully titrated, these prostaglandin-associated side effects of Latisse may enhance the periorbital cosmetic appearance.

CASE REPORT

A 60-year-old, brown-eyed white female dermatologist (author DSS) prescribed herself Latisse (bimatoprost topical solution, 0.03%) for eyelash enhancement. She had no prior history of glaucoma or the use of any ophthalmic drops. Bimatoprost was applied daily to the base of the upper eyelid cilia as directed in the package insert using the disposable applicators. Three months later, after achieving significant eyelash enhancement, she decreased the daily application to 2 - 3 times per week. In the absence of any other periorbital interventions such as botulinum toxin or fillers, she also observed other distinctive changes in the periorbital area. She developed a deepening of the upper eyelid sulcus, bilaterally, with more pre-tarsal show. The fat pads in her lower eyelids diminished significantly and she noted a tightening of the skin of the lower eyelids. There was mild hyperpigmentation of the lower eyelid skin, but no darkening in the color of the iris. No conjunctival hyperemia was noted, but there was a subtle increase in fine telangiectasias of the upper eyelids. There was no evidence of upper eyelid ptosis or lower scleral show. Even in the absence of eyelid makeup (mascara, eye liner, eye shadow), it was obvious to others that there was a dramatic change in the appearance of her eyelids and she was often asked if she had undergone a surgical blepharoplasty (Figure 2).

FIGURE 2. 60-year-old woman (author DSS) before using Latisse (Left) and 3 months after daily application of Latisse to the upper eyelid margins bilaterally (Right). Note the following changes to the periorbital areas bilaterally beyond eyelash enhancement: deepening of the upper eyelid sulcus, improvement in hooding of the upper eyelid, involution of dermatochalasis in the upper and lower eyelids, periorbital fat atrophy and tightening of the lower eyelids. In the authors' opinion, she has an overall rejuvenated appearance due to a bilateral bimatoprost-induced "chemical blepharoplasty."



DISCUSSION

Prostaglandins are lipid compounds derived enzymatically from fatty acids. They are hormone-like substances that have numerous physiologic functions throughout the human body. Bimatoprost and other similar medications are synthetically derived prostaglandin F2 alpha (PGF2 α) analogs (PGAs) that have long been used to treat glaucoma. They reduce intraocular pressure by both increasing the outflow and decreasing resistance to outflow of aqueous fluid from the eyes. When used to treat glaucoma, in addition to this intended therapeutic effect, they also have a number of other side effects. Many of these side effects have been grouped together under the name PAP – prostaglandin associated periorbitopathy. PAP was first noted in cases of unilateral glaucoma; patients complained of a difference in the appearance of their periorbital areas. When PAP ensues in the unilaterally treated eye, the patient appears disfigured because of gross asymmetry. Nonetheless, on close inspection, one can argue that in many cases the treated eye appears more youthful – with more pre-tarsal show, resolution of dermatochalasis, and reduction of pseudoherniated periorbital fat (Figure 1).

The onset of PAP can be quite rapid – within a week's time⁷ – but may also take weeks, months, or longer to develop. Not only can the onset be variable in time, but the onset may be different from one eye to the other.⁷ The clinical features of PAP also seem to be reversible – either partially or fully – with discontinuation of treatment. Some authors feel that the duration of therapy is a factor in partial or full recovery and others postulate as yet unknown factors.^{1-3,5,6}

The mechanism of action for bimatoprost causing PAP and other side effects is multi-factorial. It seems to act upon hair,

melanin, fat, and possibly skin and smooth muscle as well. The mechanism for induction of hypertrichosis seems to be a binding to prostaglandin receptors on hair follicles and increasing the percentage of hairs in anagen phase, increasing the duration of anagen phase, decreasing the duration of telogen phase, increasing the size and thickness of the dermal papilla (hair bulb), and stimulating pigment cells in hair follicles and skin.^{8,9} Obviously, with such an effect on hair growth, the potential for current or future use to increase eyebrow hair, scalp hair, and body hair warrants further research and development.

"If treatment is initiated it is important to observe patients closely for signs of PAP in order to diminish or prevent complications."

Another side effect of bimatoprost is hyperpigmentation of the iris and the skin; in both, it has been shown to stimulate melanogenesis, but the exact mechanism is unknown. In the iris, melanin granules are retained in the melanocytes and the darkening of the iris is irreversible or very slowly reversible over a long period of time.¹⁰⁻¹² Iris hyperpigmentation is more likely to occur in greenish or hazel-colored eyes; brown pigment near the pupil spreads concentrically towards the periphery of the iris. Stjernschantz, et. al. postulated some up-regulation of tyrosinase gene transcription as a possible mechanism of action for the iris pigmentation.¹⁰

The hyperpigmentation of periocular skin also seems to be related to an increase in melanogenesis. Histopathological

FIGURE 3. 88-year-old man with glaucoma. He was treated with bimatoprost in the left eye only for 8 years. The left side has PAP, but looks “better” with less bulging of the lower eyelid fat pad due to periorbital fat atrophy. (Photo courtesy of Dr. Stanley Berke)



studies demonstrate a marked increase in the number of melanin granules and an increase in the number of melanosomes in both the melanocytes and keratinocytes of bimatoprost-treated specimens compared to control (non-bimatoprost treated skin). This was in the absence of melanocyte proliferation or atypia.¹¹ Hyperpigmentation of the eyelid skin, however, seems to be reversible. Because the dermal melanocytes communicate with and transfer melanin granules to keratinocytes in the epidermis, the pigment is turned over and with discontinuation of the drug, the periorbital hyperpigmentation resolves.^{11,12}

Although the hyperpigmentation of the iris and periorbital skin may be perceived as an untoward side effect or complication of PGA treatment, a possible benefit of this increase in melanogenesis may be its potential to re-pigment vitiligo and hypopigmented scars.¹³

The most significant causative factor in the constellation of findings known as PAP is the action of bimatoprost on fat. Currently, it is thought that atrophy of the preaponeurotic and deep orbital fat is most likely responsible for the majority of the PAP changes. Fat atrophy explains the relative enophthalmos, deepening of the upper eyelid sulcus, involution of dermatochalasis, and loss of lower eyelid fullness that is due to pseudoherniation of periorbital fat (Figure 3). The PGF2 α or PGA molecule binds to the prostaglandin F2 alpha receptor (FP receptor) on preadipocytes. A complex series of reactions is initiated that results in inhibition of adipocyte differentiation and a decrease in fat accumulation within adipocytes; this eventuates in fat atrophy¹⁴⁻¹⁶ (Figure 4).

Park, et. al. showed additional histologic evidence from patients treated unilaterally with PGAs. In biopsy specimens of eyelids from both the treated side and the untreated side, they showed that the former had smaller-sized individual adipocytes and an increase in the mean adipocyte density with a higher total number of adipocytes per microscopic field. This is because the individual fat cells were smaller. There were clumped nuclei suggesting adipocyte atrophy and no significant signs of inflammation.¹⁷

FIGURE 4. Mechanism of Action of Adipose Changes in PAP: PGF2 α and PGAs bind to the Prostaglandin F receptor (FP2 α) on orbital preadipocytes and activate mitogen activated protein kinase. This results in phosphorylation and inactivation of peroxisome proliferator activated receptor gamma, causing an inhibition of adipocyte differentiation, a decrease in lipoprotein lipase levels (a marker for adipocyte differentiation), and a decrease in fat accumulation within adipocytes. (From Jayaram A. Prostaglandin Associated Periorbitopathy. http://eyewiki.aao.org/Prostaglandin_Associated_Periorbitopathy. Accessed July 28, 2014.)

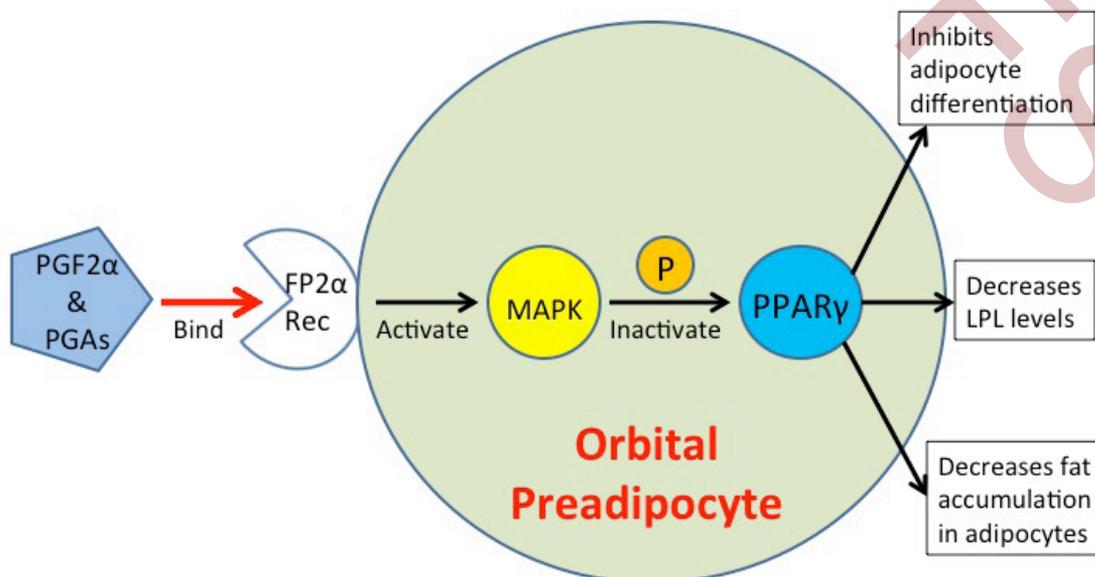


FIGURE 5. 67-year-old woman treated for glaucoma of the right eye only with PGAs for 15 years. Chronic use of bimatoprost can lead to severe PAP including upper eyelid ptosis and inferior scleral show which can be clinically significant and cosmetically disfiguring. (Photo courtesy of Dr. Stanley Berke)



MRI studies demonstrate periorbital fat atrophy in patients on bimatoprost and also demonstrate reversal of atrophy with cessation of the drug.¹⁸ In addition to the orbital fat atrophy, the MRI scans also show the resultant enophthalmos. The authors speculate on the possible use of bimatoprost or similar PGAs for “medical decompression” of exophthalmos associated with hyperthyroidism.

All of this work has been further supported by the *in vitro* work of Choi et al, who demonstrated the effects of four different PGAs (latanoprost, travoprost, bimatoprost, and tafluprost) on human orbital preadipocyte differentiation and intracellular lipid storage. Genetic markers for adipogenesis, adipocyte differentiation and intracellular lipid storage were assayed and showed a down-regulation of all three. Of the four PGAs, bimatoprost showed the greatest inhibition of adipogenesis.¹⁹

Some authors have postulated other mechanisms for PAP such as the PGA effect on the levator or Müller’s muscles, PGA-mediated reduction in collagen fibers in the levator complex or PGA-mediated collagen decomposition and levator dehiscence; these remain to be elucidated.^{1,2,20-22}

When bimatoprost is placed on the skin of the upper eyelid margin to stimulate hypertrichosis, all of the clinical findings and side effects noted with intraocular application can be seen. It can lower intraocular pressure,²³ increase iris and lid pigmentation, and cause hair growth outside of the treatment area. There is significant absorption in the surrounding periorbital tissues and this is likely responsible for the changes seen in PAP. Pharmacokinetic studies of a single topical ocular administration of 0.1% bimatoprost in male cynomolgus monkeys indicate that eyelid specimens contain more than 2,000 times the concentration of bimatoprost compared with aqueous and more than 16 times the concentration compared with iris and ciliary body. Thus, there is significant periorbital absorption of PGAs.²⁴

When Pasquale and Berke initially described PAP, it was more easily recognized in patients treated unilaterally because the asymmetry and cosmetic disfigurement was readily apparent. With bilateral use for glaucoma or hypotrichosis, these changes may be less obvious, but will likely develop nonetheless. We feel that physicians can take advantage of these characteristics if bimatoprost is prescribed for the appropriate candidates, used bilaterally and titrated with care. In addition to longer and darker eyelashes, bimatoprost can be used for a chemical blepharoplasty. It improves hooding and results in involution of dermatochalasis of the upper eyelids, creates a more prominent upper eyelid sulcus, increases pre-tarsal show, diminishes bulging lower eyelid fat pads, and tightens periorbital skin. In addition, it can make the eyes appear larger – all attributes that are associated with beauty.

The potential disadvantages of bimatoprost include the risk for hyperpigmentation of the iris and periorbital skin, increased hyperemia and periorbital erythema, and enophthalmos with a sunken, hollow orbit. Chronic use can lead to upper eyelid ptosis and inferior scleral show (Figure 5). Therefore, candidates must be chosen wisely; Latisse (bimatoprost 0.03%) should not be prescribed for patients who already have “deep set eyes” (a deep upper eyelid sulcus), those who have had a blepharoplasty with periorbital fat resection, and people who have green or hazel-colored eyes – unless they are willing to accept the possibility of iris darkening. In addition, people with age-related or hereditary periorbital fat atrophy and levator dehiscence are not good candidates for PGAs.

Not everyone with ciliary hypotrichosis is a candidate for Latisse. It is important to examine your patient carefully and document with pre-treatment photographs. Is there hooding or a hollow appearance? Is there a deep upper eyelid sulcus? Is there pseudoherniated periorbital fat in the upper or lower eyelids? Is there dermatochalasis of the upper or lower eyelids? What color are the eyes? PAP should be included in the pre-treatment discussion of PGA use for eyelash enhancement.

The best candidates are those who have dermatochalasis of the eyelids, hooding of the upper eyelids, and puffiness of the upper or lower eyelids from pseudoherniated periorbital fat. Other potential candidates are Asians who want a more westernized appearance without surgery. Approximately 50% of Asians are born with a “monolid” and 50% are born with a supratarsal crease.²⁵ Bimatoprost can be used instead of surgery in a monolid individual to create a “double eyelid.”²⁶

If treatment is initiated it is important to observe patients closely for signs of PAP in order to diminish or prevent complications. Both frontal and lateral pre-treatment and intra-treatment photographs should be taken to document eyelash enhancement and any periorbital changes that occur. In order to capture these periorbital changes, the patients must have their eyes open in

the photographs. The “sweet spot” is achieving a more youthful appearance by eliminating hooding and dermatochalasis in the upper eyelids, increasing pre-tarsal show, and diminishing bulging fat pads in the upper and lower eyelids. When deepening of the upper eyelid sulcus and diminishing dermatochalasis of the upper and lower eyelids are noted, it is advisable to reduce treatment from daily to 2-3 x per week. If complications are noted, such as ptosis or inferior scleral show, appropriate titration or discontinuance of the drug is warranted.

Other potential future uses for PGAs may be on the horizon. Of interest, a company called Topokine Therapeutics® is investigating topical bimatoprost for localized subcutaneous fat reduction by direct application on the skin of the lower eyelids, submental area and abdomen.

Today, there is increased patient demand for non-invasive alternatives to surgery. Just as soft tissue augmentation can replace cheek and chin implants, fillers in the nose can be used to achieve a “non-surgical rhinoplasty,” and botulinum toxin can be used to induce a “chemical brow lift,” topical bimatoprost holds promise as a potential agent for achieving periorbital rejuvenation beyond eyelash enhancement – a “chemical blepharoplasty.”

This is the first report of which we are aware describing the rejuvenating effect of Latisse on the periorbital area simulating a blepharoplasty. When used bilaterally and titrated to maintain the desired effects, without complications, bimatoprost can be beneficial beyond eyelash enhancement.

CONCLUSION

When applied topically on the eyelid margin for the treatment of ciliary hypotrichosis, prostaglandin analogs cause orbital fat atrophy and other morphologic changes to the eyelids. Physicians and patients should be aware of these side effects so that PGAs can be prescribed in appropriately selected individuals and titrated to avoid undesirable side effects. When early signs of PAP are noted, reduce the frequency of application to a “maintenance mode” of 2-3x per week to prevent the development of upper eyelid ptosis and inferior scleral show.

We would like to propose a name change from Prostaglandin Associated *Periorbitopathy* to Prostaglandin Associated *Periorbital Syndrome (PAPS)*. *Periorbitopathy* implies disease; it is not a disease. It is a constellation of clinical changes that, when taken together, in carefully selected patients, improves the appearance of the entire periorbital area. In addition, we also propose that PAPS include ciliary hypertrichosis and iris and periocular skin hyperpigmentation. Further research is warranted to determine the potential use of bimatoprost to achieve a chemical blepharoplasty – the elusive “blepharoplasty in a bottle.”

DISCLOSURES

The authors have no conflict of interests to declare.

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