A Case Report: Prostaglandin Associated Periorbitopathy in Patient with Short Term Fixed-Combination Prostaglandin Analogs Use

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Introduction

Purpose: To report, with supporting photo-documentation, a case of travoprost-induced prostaglandin-associated periorbitopathy (PAP)[4].

Case Report: Retrospective and observational chart review with photo-documentation of clinical features of prostaglandin-associated periorbitopathy resulting from fixed-combination of 0.004% travoprost and 0.5% timolol use. Our report shows the early onset clinical presentation of PAP[4] from travoprost. This patient developed blepharoptosis, deepening of superior fornix eyelids skin darkening, inferior scleral show and relative enophthalmos after a usage period of one month.

Conclusions: Travoprost can cause early onset of PAP[4], although many literatures suggested that it had lower severity and longer latency of onset than those with bimatoprost. Besides cosmetic appearance problems, PAP[4] also involves in uncontrolled elevated intraocular pressure (IOP)[2] from tight lid syndrome and inferior visual field defect from ptosis. Clinicians should be aware of these side effects and monitor for signs periodically and inform each patient about them before prescribing especially in all cases of unilateral glaucoma.

Keywords: PAP, Prostaglandin, Latanoprost, Bimatoprost, Travoprost, Ptosis, Orbital fat atrophy

Introduction

Presently there are prostaglandin analogs and prostamide in clinical use, including 0.005 % latanoprost (Xalatan®)[24], 0.004% travoprost (Travatan®)[22], 0.03% bimatoprost (Lumigan®)[9], 0.12% and 0.15% unoprostone (Rescula®)[19]

A newest drug, 0.0015% tafloprost (Taflutan®, Saflutan®, Taflotan® and Tapros®)[8], had also been introduced to this group. Hollo and Aihara have highlighted the fact that[6] these groups of most efficacious ocular hypotensive agents are now generally considered as reasonable for first-line treatments.

One of these ocular adverse effects that should be concerned by all ophthalmologists is Prostaglandin-Associated Periorbitopathy (PAP).[4] The former name of PAP[4] was Deep Superior Sulcus Syndrome, with acronym DUES standing for Deepening of Upper Eyelid Sulcus.[4]

This case report shows an early onset of clinical presentation of PAP[4] from fixed-combination of 0.004% travoprost and 0.5% timolol (Duotrav®)[13]

Case Report

A 50-year-old Thai woman came into Thammasat Eye Center's outpatient department with chief complaint of an acute redness and blurred vision in the left eye for one week.

Her symptoms also included headache and nausea vomiting. The underlying disease was dyslipidemia. She had no family history of glaucoma and never received any ocular surgery or eye trauma before. She denied any history of long-term steroid usage via all route.

The first eyes examination revealed that her visual acuity (VA)[2]was 20/70 PH[2] 20/20 in the right eye and 20/70 PH NI[2] in the left eye. The intraocular pressure (IOP)[2] were 24 mmHg in the right eye and 36 mmHg. in the left eye. The right cornea was clear, but left had generalized microcystic edema with scattered iris pigment at the endothelium. Both anterior chambers were shallow centrally and peripherally.

Gonioscopic examination revealed both angles were closed grade 0 according to Modified Shaffer grading classification system[10] with high peripheral anterior synechiae (PAS)[10] around 270 degrees in the right eye and 360 degrees in the left eye. Pupils were 3 mm with normally react to light in the right eye and 6 mm with semi-dilated configuration in the left eye. She had mild nuclear sclerosis in both eyes. Right cup disc ratio was 0.8 and Left cup disc ratio was 0.7. Both macula and retina were normally examined.

The first impressive diagnosis in this case was acute angle closure glaucoma (AACG)[1]with pupillary block (PB)[10] in the left eye and chronic angle closure glaucoma (CACG)[3] in the right eye.

The definite treatment in this case was laser peripheral iridotomy (LPI)[7]. This patient had received LPI[7] to both eyes and she was treated with planned phacoemulsification with intraocular lens implantation with goniosynechialysis[15] by Barkan surgical goniolens[15] in the left eye.

The eyes examination in one-week follow-up visit after LPI[7] to both eyes revealed that VA[2] were improved to 20/30 PH[2] 20/20 in the right eye and 20/20 in the left eye. Intraocular pressure in the right eye were 14 mmHg and 30 mmHg in left eye, which was still high even with many hypotensive medication usages.

Repeated gonioscopic examination were the same. The current medications included 3 antihypertensive and 1 anti-inflammatory medication 1% Pred forte left eye every 2 hours, 0.15% Brimonidine P left eye 3 times a day, Brinzolamide both eyes twice a day, she was considered for additional fixed-combination of 0.004% travoprost and 0.5% timolol (Duotrav®)[13] left eye before bed.

Three-week after the additional treatment of this fixed-combination antiglaucoma agent, the clinical of prostaglandin-associated periorbitopathy in the left eye was obviously observed as figure 1.

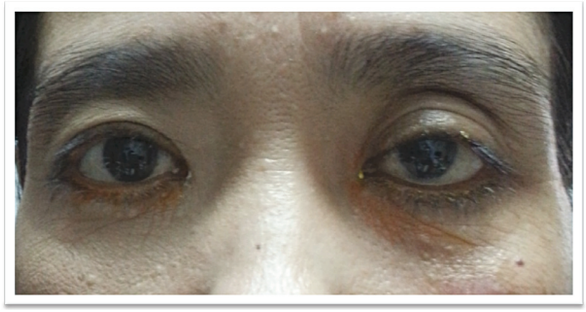

Figure 1 The left eye has upper lid ptosis, MRD_1^2 were + 3 mm and MRD_2^2 were + 6 mm, and compared with right eye, MRD_1^2 were + 5 mm and MRD_2^2 were + 5 mm. We also found deep superior fornix, inferior scleral show, periorbital tissue darkening, mild increased prominent of lid vessels and mild lid skin thickening. Suspected clinical diagnosis was PAP^4 from fixed-combination of 0.004% travoprost and 0.5% timolol usage.

Planned phacoemulsification with intraocular lens implantation with goniosynechialysis[15] was done urgently and all antiglaucoma medications were stopped postoperatively.

Postoperative eye examination revealed VA^2 was improved to 20/20 in the left eye. The intraocular pressure was decreased from 21 to 10 mmHg without any additional antihypertensive medications.

We followed clinical of PAP^4 closely after she had stopped all antiglaucoma medications including the prostaglandin analog. The clinical presentation and severity of PAP^4 had slowly improved on 1st week , 4th week and 10th week postoperative treatment follow-up, as shown in figure 2 and 3.

Figure 2 An obvious improvement of the severity of PAP^4 in the left eye. Upper lid ptosis was improved and eye lid skin thickening and darkening were improved. Deep superior fornix was improved.

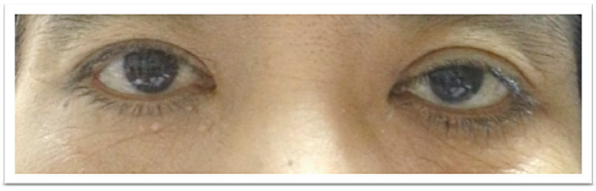

Figure 3 On the 4-week postoperative treatment follow-up, the presentation of PAP^4 had gradually disappeared nearly normal when we compared with the right eye.

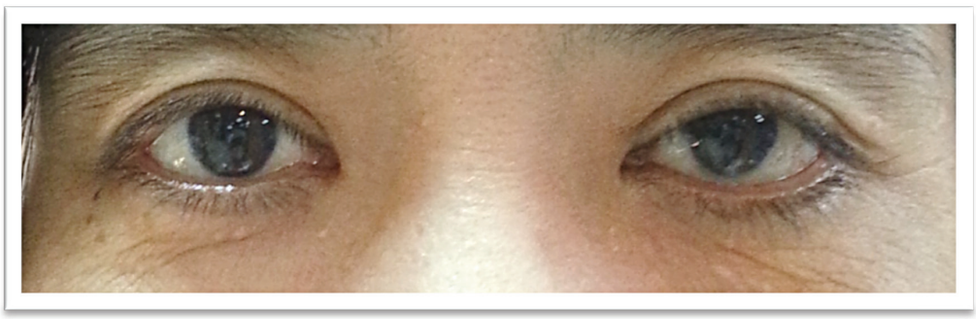

Figure 4 On the 10-week postoperative treatment follow-up, presentation of PAP^2 had almost completely disappeared.

Discussion and conclusion

This paper shows you an example of the clinical presentation of PAP^4, which is a common side effect of prostaglandinanalogs. Now medication treatment in glaucoma, first-line options include prostaglandins and beta-blockers[23] depending on issues such as cost, efficacy, diurnal benefit and compliance.[6]

Because of prostaglandin analog's efficacy and considerable convenience of these once-daily antiglaucoma drugs, we usually choose them as the first-lined treatment of POAG and OHT in the term of no contraindications.[6]

As we know prostaglandin analogs have the most efficacy in IOP^2 lowering when we compare with other groups of antihypertensive drugs.[6]

In the part of systemic or ocular side effects, beta-blockers also have been associated with many adverse events such as corneal epithelium toxicity, nocturnal hypotension, breathing difficulties, depression, erectile dysfunction, and they are contraindicated in patients with asthma, chronic obstructive pulmonary disease and some type of heart disease.[21] Furthermore, timolol does not reduce IOP^2 very effectively in patients taking higher systemic doses of propranolol or metoprolol.[21]

Because PGF_{2alpha}'s mechanism is not a highly selective agonist for the FP-receptor and can stimulate some specific EP-receptors, such as EP2 and EP4 receptors, which increase outflow facility from uveoscleral outflow and trabecular meshwork respectively and also mediate ocular inflammations.[6] For this reason, we can expect PGF_{2alpha} to have greater potential effects than the FP selective agonists used today while can also lead to greater occurrence of ocular side effects.

The adverse effects of prostaglandin groups can be happened in many parts of eyes, which include eyelid, periorbital fat, ocular surface, iris, anterior chamber reaction and posterior segment of the eyes such as macula. All the adverse effects of prostaglandin analogs were shown in the box below.[17]

Blurred vision

Stinging, itching, foreign-body sensation

Conjunctival hyperemia

Increase pigmentation of the iris and periorbital skin Longer, darker, and thicker lashes

Punctate epithelial keratopathy

Cystoid macular edema

Reactivation of herpetic infection

Facial rash

The adverse effects of prostaglandin analogs According to Asia Pacific Glaucoma Guidelines, 2008.[17]

The term prostaglandin-associated periorbitopathy, now commonly known, is developed by prostaglandin analogs. The clinical of deepening of upper lid sulcus from bimatoprost was first introduced by Peplinski LS et al. in 2004.[12] After the introduction, many glaucoma specialists started to inspect, learn and report the presentation of this periorbitopathy after prostaglandin analogs usage.

In 2012, Dr. Berke had listed the clinical presentation of PAP[4] in his interview[4] and these include upper lid ptosis, relative enophthalmos, inferior scleral show, periorbital fat atrophy, involution of dermatochalasis, deepening of the upper lid sulcus, increased prominence of lid vessels and tight eyelids.

These figure 4 and 5 are an example of the patients with PAP[4] presentation in our glaucoma clinic at Thammasat Eye Center's out-patient department.

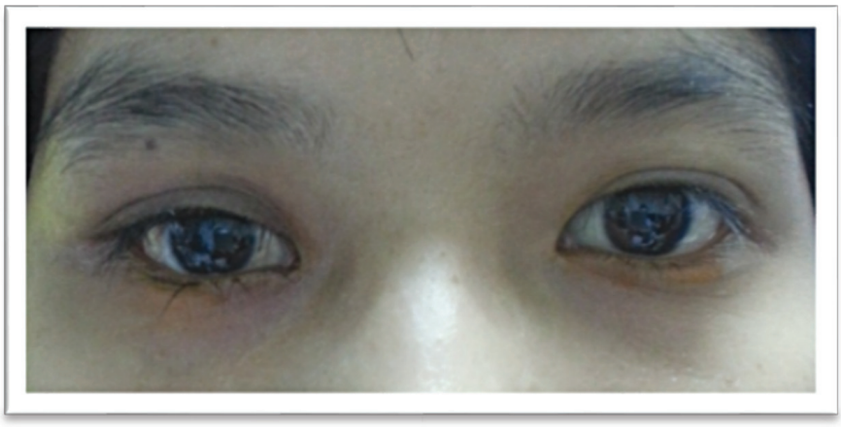

Figure 5 This young female with unilateral secondary glaucoma from retinal surgery presented prostaglandin-associated periorbitopathy in the right eye.

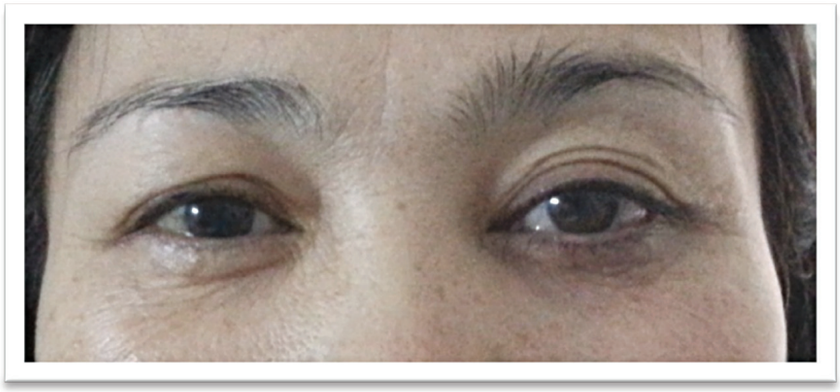

Figure 6 This middle-age female with unilateral secondary glaucoma from chronic cytomegalovirus anterior uveitis presented prostaglandin-associated periorbitopathy in the left eye.

Presently, the exact onset of PAP[4] is still unknown. In 2004, Peplinski LS et al. reported the earliest clinical presentation of PAP[4] was seen in patients who had been receivingbimatoprost for one month.[12]

Park J et al had revealed[11] mean duration of PAP[4] clinical presentation after topical usage was 2.4 ± 0.8 years in bimatoprost users, 4.8 ± 2.3 years in travaprost users, and 5.9 ± 3.6 years in latanoprost users in 2011.

We have chosen and presented the clinical of PAP[4] of this case because of its early onset of clinical presentation. As the review of clinical presentation of prostaglandin analogs shows, the onset of PAP[4] varies depending on the patient and type of PGA used.[4]

Although the cause of PAP[4] is still unclear, we found many reports about hypothesis causing each clinical presentation. One mechanism of periorbital fat atrophy may come from effects on periorbital adipocyteswas the first introduced by Filippopoulos et al. in 2008.[5]

The severity of PAP[4] have been found in bimatoprost more than travoprost and latanoprost respectively, which supported by Dr. Berke.[4,20]

For travoprost, one report from Japan reviewed 2 cases of unilateral glaucoma with clinical PAP[4] from travoprost monotherapy for 2 years and returned to normal after discontinuation of travoprost in 15 months.[14,25]

For the improvement of this symptom, we have been observing obvious improvements of some PAP[4]'s clinical presentation after this patient had discontinued this fixed-combination of travoprost. There is some improvement of deepening upper lid sulcus, ptosis and eyelid skin darkening. We want further follow-up visits to observe the improvement of these clinical presentation.

Because we do not have many reportson the onset of PAP[4] from either travoprost monotherapy or fixed-combination, we still have to find out why it caused the early onset of PAP[4] in this patient. Does this effectalso involve in the combination of timolol? Does it have other risk factors? Can we expect complete recovery from these symptoms? If the answer is yes, how long is the recovery?

Ophthalmologists should be aware of the fact that none of the drugs are the best. This is necessary in unilateral glaucoma in cosmetic appearance aspect, tight eyelid due to causing lid tightening and carefully weighed in those patients with inferior visual field loss as the development of upper eyelid ptosis artifact.[16]

Informing and making patients understand about their disease are very important, followed by choosing the right antiglaucoma drugs that can vary vastlyin each patient.

The right drug is not to be determined only by its cost and efficiency, but also the suitability of the drug for each unique patient. Also, the severity of glaucoma, including type and concentration of active gradients and preservatives, efficacy in IOP^2 lowering that compatible with target IOP^2 lowering determined by the severity, tolerated side effects and contraindications, of which can all produce good persistence and adherence of drug usage and proceeding to the best quality of life, should also be taken into considerations.

These are just a part of glaucoma medication that has significant impact in successful treatment. Coping with glaucoma, after all, may just boil down to the arts of communication and prescription.

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รายงานผู้ป่วย: ที่เกิดภาวะ Prostaglandin Associated Periorbitopathy[4] จากการใช้ยาหยอดลดความดันตาชนิด Fixed-Combination Prostaglandin Analogs

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บทนำ

วัตถุประสงค์: รายงานผู้ป่วยที่เกิด prostaglandin-assiciated periorbitopathy[4] จากการใช้ยาต้อหินชนิด fixed-combination 0.004% travoprost and 0.5% timolol

รายงานผู้ป่วย: รายงานผู้ป่วยต้อหินพร้อมประวัติโรคตาชนิดของยาที่ใช้ประกอบรูปภาพลักษณะอาการ blepharoptosis, deepening of superior fornix eyelids skin darkening, inferior scleral show จากการใช้ fixed-combination 0.004% travoprost /0.5% timolol เป็นระยะเวลาติดต่อกันนาน 1 เดือนซึ่งอาการเหล่านี้เป็นอาการข้างเคียงของยาต้อหินกลุ่ม prostaglandin เรียกว่า prostaglandin-associated periorbitopathy[4] ซึ่งนับว่าเกิดขึ้นค่อนข้างเร็วเมื่อเปรียบเทียบกับรายงานอื่นก่อนหน้านี้ [4, 5, 11, 12, 16, 18]

บทสรุป: Travoprost สามารถทำให้เกิดอาการ prostaglandin-associated periorbitopathy[4] ได้ค่อนข้างเร็วเช่นเดียวกับ bimatoprost จักษุแพทย์ควรจะตระหนักถึงอาการข้างเคียงนี้โดยเฉพาะในกลุ่มผู้ป่วยที่ต้องหยอดยาต้อหินข้างเดียวหรือผู้ป่วยที่ใช้ยากลุ่มนี้มานานและเริ่มเกิดอาการ relative enophthalmos โดยไม่ทราบสาเหตุ หรือผู้ป่วยที่อาการ PAP[4] เป็นมากจนเกิดภาวะ tight lid syndrome ทำให้มีความดันตาสูงขึ้นและไม่สามารถควบคุมความดันตาได้ด้วยยา

คำสำคัญ: PAP, Prostaglandin, Latanoprost, Bimatoprost, Travoprost, Ptosis, Orbital fat atrophy