Periorbital Changes associated with Topical Prostaglandins Analogues in a Hispanic Population

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Objective: To describe the prevalent side effects of prostaglandin analogues (PA) in a Hispanic population and their effect on quality of life (QOL).

Patients and Methods: This is a cross-sectional study conducted in a tertiary medical facility in which patients were evaluated in a single visit. Total of 14 participants in the study, 10 women and 4 men. Ages ranged from 26-78 years old. Subjects underwent a single full Oculoplastic evaluation by two physicians; one was blinded on patient medical history and assessed for PA side effects. After evaluation, each study subject was asked to answer a self-reported QOL questionnaire.

Results: Study participants had used or were currently using Bimatoprost (28.6%), Latanoprost (50%) or Travoprost (21.4%). After evaluate periorbital changes, 2 patients (14.3%) had ptosis, 2 (14.3%) had periorbital skin hyperpigmentation, 11 (78.6%) had periorbital fat show, 11 (78.6%) had eyelash elongation, 1 (7.1%) had injected conjunctiva, 5 (35.7%) had iris hyperpigmentation. 10 (71.4%) noted changes in the size/shape of their eyes. The questionnaire show that 10 (71.4%) disliked how their eyes looked. 9 (62.4%) reported dry eyes, 3 (21.4%) noted increased need to blink, 5 (35.7%) reported foreign body sensation, 7 (50%) reported burning sensation, 2 (14.2%) reported secretions and 3 (21.4%) reported sticky eyes. Mean QOL was 3.50, 2.14, and 2.00 in the Bimatroprost, Latanoprost, and Travoprost users respectively.

Conclusion: QOL questionnaire showed that Bimatoprost side effects had the most negative impact in QOL, followed by the Latanoprost and Travoprost groups. [*P R Health Sci J 2017;36:218-222*]

Key words: Prostaglandin analogues, Quality of Life, Periorbital

Prostaglandin analogues (PA) eye drops have been used since 1996 to decrease intraocular pressure in patients with open angle glaucoma and other causes of intraocular hypertension. These drugs have become the first line of therapy for glaucoma patients. Several side effects have been described with the use of these eye drops. Deepening of the upper eyelid sulcus due the use of PA was first reported by Peplinski and Smith (1) in 2004. This was initially reported with the use of Bimatoprost. Later in 2014, Kucukevcilioglu and coworkers (2) described deepening of the upper eyelid sulcus in other PA, such as Latanoprost and Travoprost. Other studies describe different side effects of PA, such as conjunctival hyperemia, elongation and darkening of eyelashes, induced iris darkening, and periocular skin pigmentation (3-5). Filippopoulos, et al. (6), mentioned side effects, such as foreign body sensation and dry eye symptoms. PA help decrease intraocular pressure by increasing outflow through the uveoscleral pathway (7). Side effects from topical PA are attributed mainly to the pro-inflammatory effect of prostaglandins; complications related to hyperpigmentation are due to increased synthesis of melanin in the melanocytes by prostaglandins (8). Quality of life (QOL) has been studied previously in glaucoma patients but with a different focus. Takahashi and peers (9) studied effect of visual acuity in QOL of Japanese glaucoma patients. Camp and coworkers (10) found that dry eye symptoms directly caused by glaucoma medications affect emotional QOL negatively. To our knowledge, these side effects have not been studied in Hispanic populations. Race and ethnicity has been studied extensively in patients with glaucoma and ocular hypertension. Different types of glaucoma tend to have a higher prevalence based on ethnicity (11,12). Given that glaucoma presents differently based on the ethnicity of the patient, side effects from drugs used for its treatment may have a dissimilar prevalence and severity in different ethnic groups. This in turn can affect the patients' quality of life at a greater or lesser degree based solely

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on ethnic variations. This is relevant in clinical practice, as it can aid in counseling our patients in a more pertinent manner prior to prescribing PA. We intend to describe the prevalent side effects in our study population consisting of Hispanic patients exclusively. Our specific aim is to evaluate how the periocular side effects of PA affect quality of life (QOL) in glaucoma patients. In this article, we present the findings of fourteen patients that suffered chronic side effects previously described in the literature caused by daily unilateral treatment with PA and the effect on their QOL.

Methods

This study was approved by the Institutional Review Board of University of Puerto Rico School of Medicine. An analytical cross sectional study was conducted focused on a single interview/interaction with the study subjects. For this study, a QOL questionnaire was developed (Table 1), which was validated by six faculty members of the University of Puerto Rico with specialties in general ophthalmology, cornea, glaucoma and retina. The questionnaire includes questions about the changes in the eye during the PA use. A reliability statistic Cronbach's was performed and the alpha values are all satisfactory, scoring 1.0. In order for those scores to be considered reliable, the measure would be equal or greater than 0.60 (13).

A total of fourteen patients participated in the study (ten women and four men). Their ages ranged from twenty-six years old to seventy-eight years old. At the time of participation all patients in the study are Hispanic and living in Puerto Rico (Table 2). The inclusion criterion for the study was for patients to have used or currently using a PA eye drop (Bimatoprost 0.01%, Latanoprost 0.005%, or Travoprost 0.004%) limited to one eye (previously prescribed by an Ophthalmologist other than the PI) and had to be older than 21 years of age. Patients who had used PA in both eyes at any given time in the past were excluded from the study.

All patients underwent a single full Oculoplastic evaluation by two physicians; one of them was blinded on patient medical history and was assessed for PA side effects such as deepening of the upper eyelid sulcus, periorbital skin pigmentation, eyelash elongation, foreign body sensation, and dry eye symptoms. After evaluation, each study subject was asked to answer a self-reported QOL questionnaire to aid in measuring the effect in QOL. The survey comprised of eight questions, each had three possible answers [never/rarely (0 points), sometimes (1 point), frequently/all-the-time (2 points)], and however, only one answer per question could be selected. Points for all questions were added for each patient and this was considered their "QOL index". A mean QOL index was calculated for each PA. Items in the questionnaire were evaluated according to the Fisher's exact test. *P*-values less than 0.05 were considered to be statistically significant. Computing the patients' responses to all questions created the QOL index. A Kruskal-Wallis test was conducted to evaluate the PA complications and their effect in the patients' QOL.

Table 2. Patient demographics

Variable	Categories	Frequency (%)
Sex	Female	10 (71)
	Male	4 (29)
Race	Black	5 (36)
	Hispanic	8 (57)
	White	1 (7)
Education Level	7-12 yrs.	2 (14)
	>12 yrs.	12 (86)

Table 1. Quality of life questionnaire

	Never or rarely (0)	Sometimes (1)	Frequently or always (2)
Have you noticed any difference in the shape and/or size of your eyes?			
Do you like how your eyes look?			
Do you feel your eyes dry?			
Do you feel the need to blink to see more clearly?			
Do you have foreign body sensation?			
Do you feel a burning sensation in your eyes?			
Do you have secretions or tearing?			
Do you have sticky eyes in the morning?			

Results

Two out of fourteen patients (14.3%) were noted to have periocular skin pigmentation in the affected eye (Table 3). Eleven out of fourteen patients (78.6%) were noted to have thicker, longer and darker eyelashes on the eye using PA eye drops. A comparison by the examiner of eye using the PA eye drop vs. the eye that did not use the drops resulted in: four patients having used Bimatoprost (28.6%), seven patients having used Latanoprost (50%) and three patients having used Travoprost (21.4%) (Table 3).

Of those who used Bimatoprost, one (25%) showed periorbital skin pigmentation, three (75%) had thicker, longer and darker eyelashes. The study subjects who are using or used Latanoprost, one (14.3%) had periorbital skin pigmentation; five (71.4%) had thicker, longer and darker eyelashes. Those who used Travoprost none (0%) showed periorbital skin pigmentation and three (100%) showed thicker, longer and darker eyelashes (Table 3).

After evaluating the clinical eye related effects of PA, periorbital skin pigmentation was observed in two PA; one patient that uses Bimatoprost (25%) and two

Table 3. Adverse effects in the treated eyes

		Prostaglandins (%)			
		Bimatoprost 0.01%	Latanoprost 0.005%	Travoprost 0.004%	P value*
Ptosis	None	3(75)	7 (100)	2 (67)	0.231
	Mild	1(25)	-	1 (33)	
Periorbital Skin Color	No	3(75)	6(86)	3(100)	1.00
	Yes	1(25)	1 (14)	-	
Periorbital Fat Show	No	-	2(29)	1(33)	0.538
	Severe	4(100)	5(71)	2(67)	
Eyelashes	No Change	1(25)	2(29)	-	1.00
	Thicker, Darker, Longer	3(75)	5(71)	3(100)	
Spontaneous Blinking	Normal	2 (50)	6(86)	2(67)	0.691
	Average	1(25)	1(14)	1(33)	
	Incomplete	1(25)	-	-	
Bell's phenomenon	Present	4(100)	3 (43)	1(33)	0.334
	Abnormal	-	3 (43)	1(33)	
	Absent	-	1(14)	1(33)	
Lids margin	Meibomian	-	3(43)	1(33)	0.799
	Meibomian and Telangiectasia	2(50)	1(14)	-	
	Normal	1(25)	2(29)	1(33)	
	Telangiectasia	1(25)	1(14)	1(33)	
Conjunctiva	Conjuctivochalasis	-	1 (14)	-	0.769
	Inflammation (Injected)	1(25)	-	-	
	Normal	3(75)	6 (86)	3(100)	
Cornea	Normal	1(25)	3(43)	2(67)	0.790
	Fluorescein Staining	3(75)	4(57)	1(33)	
Iris	Change	1 (25)	4 (57)	-	0.371
	Same	3 (75)	3 (43)	3 (100)	

*Fisher Exact Test

Table 4. Self reported adverse effects in quality of life

		Prostaglandins			
		Bimatoprost 0.01%	Latanoprost 0.005%	Travoprost 0.004%	P value*
Change in the eye's shape/size	Never or rare	-	2 (29)	2(67)	0.168
	Sometimes/always	4(100)	5 (71)	1(33)	
Like how the eyes look	Never or rare	4(100)	4 (57)	2(67)	0.357
	Sometimes/always	-	3 (43)	1(33)	
Dry eye	Never or rare	2(50)	2 (29)	1(33)	0.790
	Sometimes/always	2(50)	5 (71)	2(67)	
Need to blink many times	Never or rare	3(75)	6 (86)	2(67)	1.00
	Sometimes/always	1(25)	1 (14)	1(33)	
Foreign body sensation	Never or rare	3(75)	4 (57)	2(67)	1.00
	Sometimes/always	1(25)	3 (43)	1(33)	
Burning sensation	Never or rare	2(50)	4 (57)	1(33)	1.00
	Sometimes/always	2(50)	3 (43)	2(67)	
Feeling secretions	Never or rare	2(50)	7 (100)	3(100)	0.099
	Sometimes/always	2(50)	-	-	
Sticky eye	Never or rare	2(50)	6 (86)	3(100)	0.365
	Sometimes/always	2(50)	1 (14)	-	

*Fisher's exact test

patients that use Latanoprost (28.5%). Only one patient (25%) presented sunken eyes and uses Bimatoprost. Eyelashes' changes are observed in the three PA, where three patients used Bimatoprost (75%), five patients used Latanoprost (71.4%) and three patients used Travoprost (100%). However, this difference was not statistically significant. In terms of spontaneous blinking one patient that uses Bimatoprost (25%) presented incomplete spontaneous blinking. The Bell's phenomenon is normal in nine patients, where four are Bimatoprost user (100%), four are Latanoprost users (57.1%) and one patient is Travoprost user (33%). In reviewing the PA effects on lid margin, telangiectasia is present in two Bimatoprost users (50%), one Latanoprost user (14.3%) and in one Travoprost user (33%). In respect to conjunctiva, one Latanoprost user had conjuctivochalasis. A single patient from the Bimatoprost and the Latanoprost group presented with injected sclera. Fluorescein staining was seen in three, five and one patients from the bimatoprost, latanoprost and travoprost groups respectively.

Overall, a greater percentage of patients in the Bimatoprost group noticed a change in the size/shape of their eyes when compared to the latanoprost group, while in the travoprost group only one patient (33%) complained (Table 4). The Bimatoprost group disliked how their eyes looked the most (100% of the patients), 57.1% of Latanoprost users and Travoprost the least with 33%. 71.4% of Latanoprost users complained of dry eye symptoms, 67% and 50% of the Travoprost and Bimatoprost groups respectively, this correlates directly with the foreign body sensation complaints. Increased need to blink was noticed more on the Travoprost group (33%), followed by Bimatoprost (25%) and Latanoprost (14.3%) users. Travoprost users (67%) noticed burning sensation more than their Bimatoprost (50%) and Latanoprost (42.9%) counterparts. Secretions and eyelid crusting were reported by 50% of the Bimatoprost users. Only one of the Latanoprost users reported sticky eyes (14.3%). A

mean of QOL effect was calculated for each PA. Bimatoprost eye drops were noted to have the most significant effect in QOL as evidenced by a QOL mean of 3.5, compared to 2.0 in the Travoprost group and 2.14 in the Latanoprost users (Table 5).

Table 5. Comparison of quality of life mean by Prostaglandins

	Patients	Mean of QOL	Minimum	Maximum	Kruskal-Wallis*	P Value*
Bimatoprost 0.01%	4	3.50	1.00	6.00	1.361	0.526
Latanoprost 0.005%	7	2.14	0.00	4.00		
Travoprost 0.004%	3	2.00	0.00	3.00		
Total	14	2.50	0.00	6.00		

*Kruskal-Wallis test

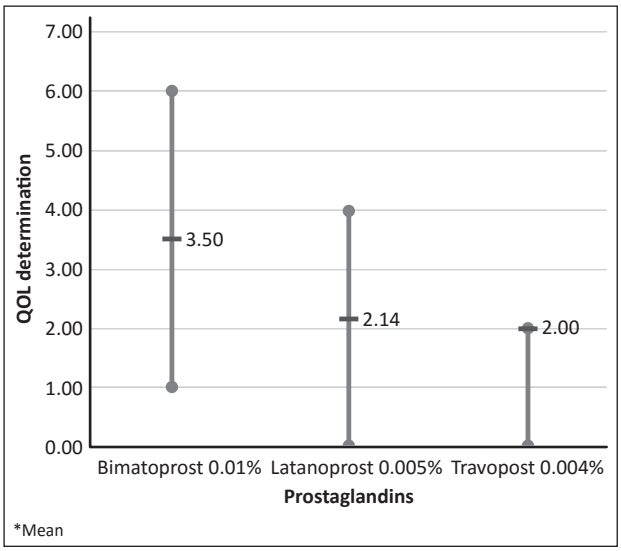

Figure 1. Index of quality of life by prostaglandin analogues

Discussion

In this group of Hispanic patients, we present evidence that chronic use of PA eye drops can be linked to periorbital changes previously described in the literature. Given the fact that our patients used PA unilaterally, they were more likely to notice changes in the size/shape of their eyes. The most common side effect noticed in our study population was eyelash elongation, changes in the size/shape of their eyes, and dry eye symptoms. Out of these patients, all except for four reported that they were not happy with the appearance of their eyes.

The quality of life questionnaire showed that in general, the Bimatoprost side effects had the most negative impact in quality of life, followed by the Latanoprost and lastly the Travoprost; however, these differences are not of statistical significance (Table 5). Bimatoprost users noted a greater difference in the size/shape of their eyes, followed by Latanoprost users, and lastly the Travoprost group. None of the Bimatoprost users liked how their eyes looked, while the Latanoprost users were the most satisfied group in terms of how their eyes looked. However, the Bimatoprost group reported having less dry-eye symptoms and foreign body sensation than the Latanoprost group. The Latanoprost patients complained the most of having dry-eye symptoms, foreign body sensation, while the Travoprost group noticed the need to blink in order to see well, and burning sensation more frequently. Latanoprost users complained the least of the need to blink in order to see well. The Bimatoprost group complained the most of having secretions, while the other two groups had no complaints. The Bimatoprost group also complained the most about eyelid crusting, followed by the Latanoprost group, while there were no complaints in the Travoprost users.

There are few studies that evaluate the QOL in patients using PA for glaucoma. Our study is unique in that it studies a Hispanic population; the focus of effect in QOL embraces dry eye symptoms as well as periocular side effects. To our knowledge, this is the first study that evaluates PAP using the subjects' contralateral eye as a control group.

After evaluating the effect on QOL of each PA, we didn't find a statistically significant difference. However, as evidenced by mean QOL, the Bimatoprost group QOL was more affected than the other two groups, followed by the Latanoprost group and lastly the Travoprost group.

Several studies have reported that stopping glaucoma treatment with PA due to their side effects is not common. However, Reardon and coworkers (14) found that compared with Latanoprost, those using Bimatoprost were 38% more likely to discontinue/change treatment and those being treated with Travoprost were 36% more likely to discontinue/change treatment. This behavior might be explained by our mean QOL, as previously described those in the Bimatoprost group had a higher mean QOL followed by Travoprost users. A more recent study by Campbell and his team (15) compared adherence in patients using Bimatoprost 0.01% vs Bimatoprost 0.03%, and found that those using the lower dose PA had higher adherence to treatment, this might suggest a dose dependent effect on mean QOL as suggested by lack of adherence, however further studies are needed to prove this hypothesis. Interestingly, Quaranta and company (16) studied seventy-five eyes using Travoprost but only five eyes discontinued the medication due to side effects. Measurement of QOL in these patients is important as it can help establish parameters in regards to discontinuing PA treatment in patients experiencing severe side effects negatively affecting QOL.

The results in this study were of no statistical significance as noted on the *p values* for the study data. Possible contributing factors for this are the low number of subjects used in the study, different number of subjects per study group, different

duration of treatment with PA for each subject, among other possible causes. Nonetheless, we believe this data will serve as a guide for the scientific community for further studies.

Resumen

Objetivo: Describir los efectos secundarios frecuentes de los análogos de prostaglandinas (AP) en una población hispana y su efecto en la calidad de vida (CDV). Pacientes y Métodos: Se trata de un estudio transversal realizado en un centro médico terciario donde los pacientes fueron evaluados en una sola visita. Había un total de 14 participantes en el estudio, 10 hembras y 4 varones. Sus edades fluctuaron entre 26-78 años de edad. Dos médicos hicieron una sola evaluación oculoplástica. Uno de ellos no tenía conocimiento de la historia clínica de los pacientes y los evaluó para determinar efectos secundarios de AP. Luego de la evaluación, se le pidió a cada sujeto del estudio responder a un cuestionario de CDV. Resultados: Los participantes del estudio habían utilizado, o estaban utilizando, Bimatoprost (28.6%), Latanoprost (50%) o Travoprost (21.4%). Después de evaluar cambios periorbitales, se determinó que 2 pacientes (14.3%) tenían ptosis, 2 (14.3%) tenían hiperpigmentación periorbital de la piel, 11 (78.6%) mostraban prolapso de grasa periorbitaria, 11 (78.6%) tenían pestañas alargadas, 1 (7.1%) tenía conjuntiva inyectada, 5 (35.7%) tenían hiperpigmentación en la iris y 10 (71.4%) observaron cambios en el tamaño/forma de sus ojos. El cuestionario reflejó que a 10 (71.4%) de ellos no les gustaba cómo se veían sus ojos, 9 (62,4%) informaron tener ojos secos, 3 (21.4%) observaron una mayor necesidad de parpadear, 5 (35.7%) informaron tener una sensación extraña, 7 (50%) reportaron sentir ardor, 2 (14.2%) informaron tener secreciones y 3 (21.4 %) informaron tener ojos pegados. Los resultados del promedio de CDV fueron 3.50, 2.14 y 2.00 en los usuarios Bimatroprost, Latanoprost y Travoprost, respectivamente. Conclusión: El cuestionario de CDV demostró que los efectos secundarios de Bimatoprost tuvieron el impacto más negativo en CDV, seguido por los grupos Latanoprost y Travoprost.

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