ORIGINAL ARTICLE

Evaluation of Prostaglandin Analogues on Idiopathic Epiretinal Membrane Formation in Glaucoma Patients

Oksan Alpogan[1], Hatice Tekcan[2], Serhat Imamoglu[1], Meltem Toklu[3]

ABSTRACT

Purpose: To evaluate the impact of prostaglandin analogues (PGAs) on idiopathic epiretinal membrane (iERM) formation in glaucoma patients.

Materials and Methods: Fifty-five eyes of 46 patients that were diagnosed with iERM following at least 6 months of glaucoma treatment were retrospectively analyzed and included in the study group. Age and sex matched control group of 60 patients was formed from random consecutive patients who were followed up in the glaucoma unit and had no ERM. A multivariate generalized linear model for adjusted analysis including hypertension, diabetes, pseudophakia, and different kinds of glaucoma medication was used to test the differences between the groups. Logistic regression (LR) analysis was used in the multivariate evaluations of the effects on iERM.

Results: The use of PGAs was significantly higher in iERM group (p = 0.009). The use of Dorzolamide in the iERM group was significantly lower than that in the non-ERM group (p = 0.044). The coexistence of PGA use and systemic hypertension (HT) was significantly higher in the iERM group (p=0.035). The effect of PGAs was found to be statistically significant, and the odds ratio of its effect on iERM was found to be 2.932 (95% confidence intervals: 1.295-6.639, p=0.01) times in the LR analysis.

Conclusions: The use of dorzolamide was significantly higher in the non-ERM group. The use of PGAs was significantly higher in the iERM group. Also, there was a significant relationship between PGAs and iERM formation.

Keywords: Idiopathic epiretinal membrane, Glaucoma, Prostaglandin analogues, Dorzolamide.

INTRODUCTION

Epiretinal membrane (ERM) is characterized by fibrocellular tissue proliferation on the internal limiting membrane (ILM). The symptoms vary in severity, from the appearance of cellophane reflux without visual impairment to wrinkles and traction on the macular area that causes decreased vision and metamorphopsia. While the ERMs, whose etiology is not fully understood and without previously known eye disease, are called idiopathic ERM (iERM), those with ocular diseases such as retinal detachment, intraocular inflammation, and trauma are called secondary ERM.[1,2]

The most accepted theory about the formation of iERM is the passage and proliferation of glial cells to the superficial defects formed in the ILM as a result of posterior vitreous detachment. Although the iERM etiology is not fully known, inflammation has been suggested as the causative mechanism. The effects of cytokines and growth factors in vitreous fluid on cells such as ERM-producing glial cells, fibroblasts, hyalocytes, and their access to the retinal surface will always be the center of discussion.[3]

Prostaglandin analogues (PGAs) are powerful antiglaucomatous agents used in the treatment of glaucoma. The most common side effects of PGAs are hyperemia, changes in the eyelids, iris darkening and, periocular skin hyperpigmentation. Serious side effects such as iris cysts, cystoid macular edema, anterior uveitis, reactivation of herpes simplex keratitis are also reported, although less frequently.[4] There are some reports that macular edema (ME) is higher after cataract surgery in patients receiving topical PGAs.[5,6]

In one other study, the vitreous anatomy, which assumes the presence of direct anterior-posterior communication,

1- Assoc. Prof. Dr., Haydarpasa Numune Training and Research Hospital, Sadık Eratik Eye Clinic, Istanbul, Türkiye

2- MD, Haydarpasa Numune Training and Research Hospital, Sadık Eratik Eye Clinic, Istanbul, Türkiye

3- MD, Tatvan State Hospital, Bitlis, Türkiye

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Correspondence Address:
Okşan Alpogan
Haydarpasa Numune Training and Research Hospital, Sadık Eratik Eye Clinic, Istanbul, Türkiye
Phone: +90 532 564 2176
E-mail: oksanalpogan68@gmail.com

was discussed, and it was stated that there may be a direct transition of inflammatory agents produced in the anterior segment of the eye.[7]

The aim of this study was to evaluate the relationship of iERM development with the use of PGAs in patients with glaucoma.

MATERIALS AND METHODS

The following study was carried out in accordance with the tenets of the Helsinki declaration. Ethics Committee approval was not required for this study. However, permission was obtained from the management of Haydarpaşa Numune Training and Research Hospital for this retrospective study (62977267-000-6070).

For this study, 6200 patient files, which were followed in the retina clinic, were reviewed. ERM was present in 395 of the patients. Sixty-nine of these patients also had glaucoma and were also followed up in the glaucoma clinic. Files of a total of 69 patients diagnosed with ERM and glaucoma were analyzed retrospectively. Twenty-three cases were excluded because of secondary ERM or because they did not meet the inclusion criteria. Fifty-five eyes of 46 patients with iERM who met the inclusion criteria were included in the study.

Patients with gonioscopically confirmed open-angle who applied anti-glaucomatous drops at least 6 months before the diagnosis of iERM were enrolled in this study. The diagnostic criteria for primary open-angle glaucoma included initial IOP above 21 mmHg, characteristic glaucomatous optic nerve head changes (cup/disc ratio ≥0.6, localized marginal loss, disc bleeding or cup/disc asymmetry >0.2), glaucomatous visual field defects with computerised visual field examination (SITA Standard algorithm, 24-2 test, Humphrey Visual Field Analyzer II; Carl Zeiss Meditec). The visual field defects were confirmed by at least two reliable visual field tests (<33% false-negative and false-positive responses and <20% fixation loss). The criteria of pseudoexfoliation glaucoma was open-angle glaucoma with visible pseudoexfoliation material on the anterior segment structures with a dilated pupil. The cases without glaucomatous changes in the optic nerve head and visual field, but with baseline IOP above 21 mmHg, were defined as ocular hypertension. Hodapp classification was used to classify glaucoma.[8]

Exclusion criteria were as follows: Use of glaucoma medication after ERM diagnosis; cases with narrow-angle glaucoma; congenital glaucoma; and secondary open-angle glaucoma except pseudoexfoliation glaucoma; comorbid eye conditions that could influence the results such as inflammatory eye diseases (uveitis, endophthalmitis), retinal pathologies (retinal detachment, retinal vein occlusions, ME, diabetic retinopathy, hypertensive retinopathy, and senile macular degeneration), intraocular tumor; any history of ocular trauma or laser therapy (retinal laser photocoagulation, laser therapy for glaucoma, laser capsulotomy); history of glaucoma surgery or vitreoretinal surgery. Patients who underwent complicated cataract surgery were not included.

Sixty patients in the control group were created from randomized consecutive file folder order in the glaucoma unit (file numbers 3482-4368), matching the age and sex of the study group. Accordingly, patients who do not have ERM, and who use glaucoma medication for at least 6 months, were admitted to the control group, following the inclusion and exclusion criteria. If the left eye does not meet the criteria, the right eye was included in the study.

Glaucoma drugs of both groups were grouped according to their active ingredients. Also, combined drugs were grouped among themselves. A separate grouping was made for the glaucoma drugs used according to the number of preservatives such as cases with one preservative, cases using two or three preservative drugs. In addition, the cases were included in the evaluation for uncomplicated cataract surgery, diabetes mellitus (DM), and systemic hypertension (HT).

Spectralis optical coherence tomography (OCT)-Heidelberg Engineering (Heidelberg, Germany) were used for ERM diagnosis and retinal nerve fiber layer (RNFL) evaluation. When ERM was diagnosed, visual acuity was evaluated.

The iERM classification was as follows: Thin membrane formations on the sensorial retina were described as cellophane maculopathy, and formations in which the posterior hyaloid partially detached from the retinal surface but still remained as an unseparated and tractional part of the macula were described as vitreomacular traction (VMT).

Statistical analysis

Statistical analysis was performed using the SPSS, version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Firstly, numerical values were tested for normal distribution. An independent simple test was used for those with normal distribution and Mann Whitney *U* test was used for those without normal distribution to compare examinations between the two groups. A multivariate general linear model for adjusted analysis including hypertension,

diabetes, pseudophakia, and different kinds of glaucoma medication was used to test the differences between groups.

Pearson's chi-square test was used to compare the categoric variables in different groups. Fisher's Exact test was used in the correlation between iERM severity and PGAs. For multivariate evaluations of the effects on the iERM, backward logistic regression (LR) analysis was used, in which the use of PGAs, timolol, carbonic anhydrase inhibitors, and brimonidine and the presence of diabetes mellitus, systemic hypertension, and pseudophakia were included in the model. The values were given as mean±standard deviation and/or median with range, and a p-value <0.05 was considered as statistically significant.

RESULTS

There was co-existence of iERM and glaucoma in 11.64% (395/46) of the cases with ERM in this study.

There was no statistically significant difference in terms of the gender distribution of 46 ERM cases (20 females, 26 males) in the iERM group and 60 cases (29 females, 31 males) in the non-ERM group (p = 0.61). The average age in the iERM group was 71.60 ±4.39 years, the average age in the non-ERM group was 72.07±5.77 years (p=0.78).

The follow-up period of the cases in the Glaucoma Clinic was 7.68±2.99 years in the iERM group and 7.65±4.31 years in non-ERM (p=0.967). The iERM diagnosis was made 4.57±2.89 years after the glaucoma diagnosis. Follow-up period at the Retina Clinic for iERM diagnosis was 2.87±1.91 years. Duration of use of PGAs was 7.02±2.45 years in iERM group and 8.45±4.54 years in non-ERM group (p=0.114). Of the iERM cases, 36 (65.45%) had cellophane maculopathy and 19 (34.54%) had VMT. Of the cases using PGA, 31 had cellophane maculopathy and 12 had VMT. The correlation between iERM severity and PGAs was not significant (p=0.084).

There was no significant difference between the two groups in terms of DM (p=0.56) and HT (p=0.07) and uncomplicated cataract surgery (p=0.48). Visual acuity was significantly lower in the iERM group (p<0.0001). Macular thickness was significantly higher in the iERM group (p<0.0001) (Table 1).

Table 2 shows the distribution of glaucoma drugs by their active substances and the number of preservatives in iERM and non-ERM groups. Pearson's chi-square test and multivariate general linear model for adjusted analysis including hypertension, diabetes, pseudophakia, and different kinds of glaucoma medication were shown on Table 2. There was a significant difference between the two groups in term of PGAs use (p=0.009). Dorzolamide use was significantly less observed in the iERM group (p=0.044). No difference was observed between the two groups in any of the other drug ingredients. The number of preservatives in iERM patients was single in 29 eyes

Table 1: *Clinical characteristics and association of data.*

	ERM (n=55)	Non-ERM (n=60)	*P*
Mean age (± SD) *	71.60 (±4.39)	72.07 (±5.77)	0.788
Sex % (n)**			0.619
Male	47.2% (26)	51.6% (31)	
Female	36.3% (20)	48.3% (29)	
Visual acuity (decimal system) *	0.72±0,24	0.88±0.13	<0.0001†
Intraocular pressure (mmHg)*	15.67±3.32	16.11±2.30	0.263
Cup/Disc ratio*	0.52±0.21	0.47±0.17	0.282
Visual field (MD) (db)*	-5.80±5.32	-5.39±5.87	0.545
RNFL thickness (µm)*	90.92±19.86	88.31±19.1	0.532
Macular thickness (µm)	345.88±67.70	241.53±40.54	<0.0001†
Diabetes mellitus *% (n)***	36.3% (20)	41.6% (25)	0.561
Hypertension *% (n)***	56.3% (31)	40% (24)	0.079
Cataract surgery *% (n)***	29.1% (16)	23.3% (14)	0.48

RNFL, retinal nerve fiber layer; ERM (epiretinal membrane); iERM (idiopathic epiretinal membrane); *Mann Whitney *U* test; **Chi square test
Independent samples t test was used for other parameters; † *P<0.05*

(52.7%), two in 15 eyes (27.27%), and three in 11 eyes (20%). There was no significant difference in the number of preservatives and iERM formation between the two groups (p=0.448).

Table 3 shows topical prostaglandin use and other conditions present. The coexistence of PGAs use and HT was significantly higher in the iERM group (p=0.035).

While evaluating the risk factors affecting iERM, the statistical model was found to be significant in the backward multivariate LR analysis by including presence of diabetes mellitus, systemic hypertension, and pseudophakia, and using of PGAs, timolol, carbonic anhydrase inhibitors, and brimonidine in the model (F=7.023, p=0.008; p<0.05). The explanatory coefficient of the model (60.9%) was found to be moderate. In the model, only the effect of PGAs was found to be statistically significant, and the ODDS ratio of its effect on iERM was found to be 2.932 (95% CI: 1.295-6.639) times. The effects of other variables included in the model are not significant (p>0.05) (Table 4).

DISCUSSION

In the present study, we evaluated the impact of PGAs use on the formation of iERM in glaucoma patients. We found that the use of PGAs was statistically significantly higher in the iERM group. The use of PGAs was significantly

Table 2: *Distribution of antiglaucoma medications used*

	ERM (n=55) n (%)	Non-ERM (n=60) n (%)	*P*	*P*†
Prostaglandine analogs	43 (78.1%)	33 (55%)	**0.009***	**0.008***
Bimatoprost	17 (30.9%)	11 (18.3%)	0.116	0.119
Latanoprost	18 (32.7%)	13 (21.6%)	0.182	0.185
Travoprost	8 (14.5%)	9 (15%)	0.945	0.946
Timolol	36 (65.4%)	44 (73.3%)	0.359	0.363
Dorzolamide- Timolol	14 (25.4%)	26 (43.3%)	**0.044***	**0.045***
Brizolamide- Timolol	12 (21.8%)	7 (11.6%)	0.143	0.146
Bimatoprost- Timolol	4 (7.2%)	3 (5%)	0.451	0.614
Latanoprost- Timolol	4 (7.2%)	2 (3.3%)	0.299	0.347
Travoprost- Timolol	0	2 (3.3%)	0.270	0.175
Brimonidin- Timolol	2 (3.6%)	3 (5%)	0.541	0.723
Carbonic anhydrase inhibitors	27 (49,1%)	34 (56,7%)	0,416	0.421
Brinzolamide	13 (23.6%)	8 (13.3%)	0.153	0.156
Dorzolamide	14 (25.4%)	26 (43.3%)	**0.044***	**0.045***
Brimonidine	20 (33.3%)	23 (38.3%)	0.827	0.829
Combination antiglaucoma medication	36 (65.4%)	43 (71.6%)	0.473	0.477
Number of preservatives in antiglaucomatous medication used (1/2/3)	29(52.7%) / 15 (27.2%) / 11(20%)	38(63.3%) / 12(20%) / 9(15%)	0.448	0.913

ERM (epiretinal membrane); iERM (idiopathic epiretinal membrane); *$p<0,05$; p†, multivariate general linear model for adjusted diabetes mellitus, hypertension, cataract surgery, and different kinds of glaucoma medication.

Table 3: *Topical prostaglandin analogs use and other conditions present.*

	ERM (n=55) n (%)	Non-ERM (n=60) n (%)	*P*
Topical PGAs use and hypertension	24 (43.6%)	15 (25%)	**0.035***
Topical PGAs use and diabetes	15 (27.2%)	13 (21.6%)	0.48
Topical PGAs use and pseudophakia	11 (20%)	5 (8.3%)	0.07

ERM (epiretinal membrane); iERM (idiopathic epiretinal membrane); PGAs, prostaglandin analogs; *p<0.05

Table 4: *Risk factors for idiopathic epiretinal membrane formation.*				
	p	**OR**	**95%CI for ODDS**	
			Lower	**Upper**
Diabetes mellitus (+)	0.358	0.674	0.290	1.563
Hypertension (+)	0.101	2.004	0.874	4.598
Cataract surgery (+)	0.267	1.695	0.668	4.299
Prostaglandine analogs (+)	**0.010***	**2.932**	1.295	6.639
Timolol (+)	0.553	0.710	0.229	2.201
Carbonic Anhydrase Inhibitors (+)	0.282	1.871	0.597	5.862
Brinomidine (+)	0.985	0.992	0.423	2.326
OR, odds ratio; CI, confidence interval; *; p<0.05				

associated with iERM. Also, we found that the use of dorzolamide was significantly higher in the non-ERM group.

Prostaglandins (PG) are one of the arachidonic acid metabolites. In vivo, arachidonic acid can be metabolized to PGs, leukotrienes, thromboxane, and others via the cyclooxygenase (COX) pathway, lipoxygenase enzymes pathway, and cytochrome P450 pathway. Arachidonic acid and PGs are associated with disruption of the blood-retinal barrier and intraocular inflammation.[9] It has been demonstrated that PG E2 increases significantly in patients with proliferative vitreoretinopathy.[10] Studies have shown that COX inhibitors can prevent intraocular fibrosis by inhibiting arachidonic acid metabolites.[9] In addition, COX activity can be increased with PGs with positive feedback.[11] In the early stage of fibrosis, lornoxicam, one of the nonsteroidal anti-inflammatory drugs, can reduce retinal fibrosis by 31 and 43% with COX inhibition.[12] In addition, steroids show an anti-inflammatory effect by preventing the metabolism of arachidonic acid by inhibiting phospholipase A2.[12] Also, a study reported that PGs released by endothelial cells exhibited potent chemoattractive activity for neutrophils and macrophages in vitro.[13] These studies provide evidence that PGs are effective in inflammation and intraocular fibrosis.

PGAs are strong ocular hypotensive molecules and are often preferred in first-line therapy in glaucoma treatment.[14] Although PGAs itself is not a pro-inflammatory molecule, it has been assumed that it can regulate the synthesis of endogenous prostanoids involved in the inflammatory cascade and induce inflammation in the eye. However, there are very limited clinical studies on this subject. Clinical studies report that PGAs cause the formation of cystoid ME or uveitis due to the rupture of the blood-retinal barrier, especially in pseudophakic and aphakic eyes.[15] In a study by Cellini et al.[16], although more prominent in the latanoprost group, it was demonstrated by flare cell meter analysis that all PGAs broke the blood-aqueous barrier. In addition, many studies have reported that the topical use of prostaglandin-inhibitors, ketorolac and nepafenac reduces cystoid macular edema.[17] However, there are limited studies on the effect of PGAs on iERM in glaucoma patients.

In one study, the development of iERM with PGAs was not significant and it was stated that the use of dorzolamide could have an effect on this finding; but it was also emphasized that the number of cases were insufficient.[18] However, one study showed that topical use of dorzolamide resulted in the resorption of macular edema in patients with ERM undergoing vitrectomy and phacoemulsification. The authors reported that this was due to the anti-inflammatory effect of dorzolamide.[19] Another study investigated the effect of dorzolamide on interleukin-6 levels.[20] These studies may explain the contribution of high dorzolamide use in the non-ERM group in our study.

Many studies state that age is an important risk factor for ERM.[21,22] Therefore, the control group was matched with the study group by age in our study. Studies have also reported that DM, cataract surgery, and hypercholesterolemia are risk factors for iERM formation.[21,22] We could not find a relationship between DM and iERM in our study. Contrary to prevalence studies, the exclusion of patients with diabetic retinopathy may have affected this result. There was no significant difference between iERM and non-iERM groups in terms of HT in our study. However, the rate of systemic HT in glaucoma patients using PGAs was higher in the iERM group. Also, the coexistence of PGAs use and HT was significantly associated with iERM. Xiao et al.[23] reported no evidence of the incidence of HT

and ERM in a review. However, one study reported that PGAs can increase systemic blood pressure.[24] However, the significantly higher coexistence of PGAs use and HT may be due to less use of beta-blocker combinations due to cardiac side effects.

In a study, latanoprost has been shown to break the blood-retinal barrier and increase angiographic macular edema after uncomplicated cataract surgery in the early stage.[25] A retrospective study with PGAs states that, unlike other studies, cataract surgery does not increase the formation of iERMs.[18] We also found that cataract surgery does not increase the formation of iERM. The reason for this may be that we did not include patients who underwent laser capsulotomy and/or complicated cataract surgery in our study. However, it can be predicted that different results may be obtained in complicated surgeries.

There were some limitation in this study. The major limitation of this study was the small sample size and that it was retrospective. Also, there was no uniform medical treatment for the patients. Recently, it has been reported that PGAs may cause ME due to the preservatives they contain.[26] Although we did not have any non-preservative forms, patients were grouped according to their medications in many ways to evaluate this possibility; those who use a single preservative and those with two or three preservatives. Accordingly, we observed that the increase in preservative numbers did not affect iERM formation.

In conclusion, in the present study, a significant relationship was observed between the use of PGAs and iERM formation in glaucoma patients. However, the use of dorzolamide was higher in the non-ERM group. Therefore, besides the effect of PGA on iERM formation, it can be predicted that dorzolamide may have an inhibitory effect on iERM formation. Thus, this study should further be supported by long-term, prospective, randomized, and controlled studies with patients using PGAs.

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