

Comparison of β -Blockers and Prostaglandins Treatments in Primary Open-Angle Glaucoma

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Objectives: Retrospective study to compare long-term effects of treatment with β -blockers and prostaglandins by assessing changes in visual fields.

Methods and Patients: The group included 60 patients of approximately the same age (61 and 62 year olds), with the same changes in the visual field and the same central corneal thickness (556 μm), of which 30 were treated with β -blockers (18 females and 12 males) and 30 with prostaglandins (15 females and 15 males). There were no changes in medication in the course of treatment. During the follow-ups, the intraocular pressure was in the range 10 to 20 mmHg. We evaluated the changes in visual fields (pattern defects) at the last examination in 2012. The results were compared with findings in visual fields from 2005. No subject had any eye or systemic disease that could affect changes in the visual field. Corneal pachymetry was performed with a Tomey SP-100 ultrasound device. The visual field was examined by static perimetry using a MEDMONT M 700 device with a fast threshold glaucoma program. For comparison of the two groups treated with β -blockers and prostaglandins, we used the Mann-Whitney's test. For comparison of treatment with β -blockers timolol, carteolol, betaxozol and vistagan, we used the non-parametric Kruskal-Wallis' test, and subsequently to compare therapies with prostaglandins latanoprost and bimatoprost, we used the non-parametric two-sided Mann-Whitney's test.

Results: With statistical analysis, we have found neither changes between β -blockers and prostaglandins treatments ($p=0.395$ to 0.836) nor differences between different beta-blockers ($p=0.495$ to 0.576). Similarly, we found no statistically significant changes in either treatment with bimatoprost and latanoprost (0.575 to 0.965).

Conclusion: Our results in the follow-up period of seven years showed no difference in the functional changing of visual field between the treatments with β -blockers and prostaglandins.

Keywords: β -blockers and prostaglandins treatment; Visual field; Therapy of beta-blockers and prostaglandins

Introduction

Glaucoma is a progressive neurodegenerative disease of retinal ganglion cells (RGCs) associated with characteristic axon degeneration in the optic nerve [1]. We have previously provided evidence in several of our studies that damages do not merely include damages of retinal ganglion cells and their axons [2-5].

The main protective element of ganglion cells in hypertensive glaucoma is the reduction of intraocular pressure (IOP) [1]. IOP can be reduced in various ways. At present, the most commonly used drugs are β -blockers and prostaglandins. The study of Holmstrom et al [6], who observed the cost-effectiveness of bimatoprost, latanoprost and timolol in treatment of primary open angle glaucoma in five major European countries (France, Germany, Italy, Spain and the United Kingdom), confirms this as well. In these countries, latanoprost leads as the first-line of treatment. In four out of five of these countries, timolol with add-on latanoprost also lead as the first-line of treatment. Under a pharmaco-economic analysis, the most cost-effective strategy seems to be timolol as the first line with add-on bimatoprost if target is not met after 3 months. Based on this information, we tried to compare the effect of treatment with β -blockers and prostaglandins on changes in the visual fields. There are only few studies on the functional assessment of both types of anti-glaucomatous treatment.

β -adrenoceptor antagonists are further subdivided into the β_1 -selective (e.g. betaxolol) and non-selective (e.g. timolol) β -blockers. All β -blockers lower IOP via inhibition of β_2 -adrenoceptors present

on the ciliary epithelium, thus reducing aqueous humor flow. The neuroprotective elements of β -blockers are believed to be mediated by inhibition of calcium and sodium ion influx into neurons, which occurs in hypoxia, ischemia and excitotoxicity. NMDA and glutamate affinity is also reduced, thus further reducing calcium influx into the RGCs. Timolol binds to voltage-gated calcium and sodium channels, which in turn reduces NMDA stimulated calcium influx, however, to a much lower affinity in comparison to betaxolol. Although the systemic route is just as important as the topical route, betaxolol seems to accumulate in membranes, as it is highly lipophilic. Hence, the concentration is appreciably lower in the vitreous or retina. Correspondingly, high doses of timolol are required to be absorbed systemically. For this reason, the topical route may have a better efficacy in reducing IOP and RGC loss through absorption of timolol into systemic circulation, which plays an equally vital role [7].

It has been well accepted that prostaglandins, including PGF₂ α , are implicated in the pathogenesis of ischemic and inflammatory

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injuries. They are potent vasoconstrictors and can possibly play a role in the pathogenesis of ischemia and inflammation. However, there is currently no evidence to suggest that they are toxic to the retina or optic nerve. Drugs such as latanoprost, travoprost, bimatoprost and unoprostone enhance aqueous outflow, thus reducing IOP. Latanoprost exerts its neuroprotective effects by impeding glutamate and hypoxia-induced apoptosis and is postulated to act via negative feedback on cyclooxygenase-2 activity. Though intravitreal administration of latanoprost has demonstrated an increase in RGC survival following transection of the optic nerve, no electrophysiological data has been documented with regard to the mechanism of action. Again, there have been no large clinical trials focusing on the neuroprotective effects of prostaglandins [7].

Methods and Patients

The inclusion criteria in this study were age matched and representation of both sexes, minimal changes in the visual field at the beginning of monitoring in 2005 (pattern defects 0-4), visual acuity 1.0, refraction in the range -5 to +4 diopter, no changes in treatment during the observation period, no other eye or systemic diseases influencing changes in ocular fields, and field reliability indices less than 15%. Compared treatment groups included an identical number of patients whose should not change throughout the duration of the study.

The group included 60 patients, of whom 30 were treated with β -blockers (18 females, mean age 63.4 years and 12 males, mean age

61.3 years) and 30 with prostaglandins (15 females, mean age 58.7 years and 15 males, mean age 63.6 years).

We evaluated changes in visual fields (pattern defects-PD) from 2005 to 2012. The visual field was examined by using static perimetry MEDMONT M 700 (Medmont Pty Ltd, Australia) device with a fast threshold glaucoma program.

Corneal pachymetry (CCT) was performed on an ultrasound device Tomey SP-100 ultrasound device (Tomey, Nagoya, Japan).

Results

The measured values are shown in Tables 1 and 2.

Due to remoteness of some measurements and therefore abnormal data, the nonparametric two-sided Mann-Whitney's test was used for comparison between the two groups treated with β -blockers and prostaglandins.

Table 3 shows that the results of Mann-Whitney's test do not differ in any assessed parameter in the group of glaucoma eyes treated with β -blockers and prostaglandins.

For comparison of four therapies including timolol, carteolol, betaxozol and vistagan within the treatment with β -blockers, the nonparametric Kruskal-Wallis' test was used due to great remoteness of some measurements and therefore abnormal data. The Kruskal-Wallis' test evaluates whether different medians within each of four groups differ. The statistical analysis shows that none of the observed

gender/age	Refraction		Visual acuity		CCT um		VF PD 2005		VF PD 2012		IOP		Therapy
	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	
F/62	-2	-2	1	1	556	542	2.06	1.64	2.06	2.05	12	12	timolol
F/64	1	1	1	1	558	560	2.15	2.63	3.53	3.00	16	16	carteolol
F/70	1	2	1	1	580	580	1.65	1.35	1.88	1.37	17	17	timolol
F/61	0	0	1	1	540	544	5.88	3.02	5.90	3.05	13	16	betaxolol
F/63	-2.25	0	1	1	570	565	1.64	1.42	2.49	2.19	20	20	carteolol
F/63	0	0	1	1	540	546	2.80	2.47	2.08	1.62	13	13	carteolol
F/63	2	2	1	1	534	540	2.19	2.00	1.59	2.00	15	15	timolol
F/69	1	1	1	1	545	533	1.98	3.25	2.03	2.85	14	14	timolol
F/67	0	0	1	1	567	572	2.09	2.49	1.78	2.71	14	14	betaxolol
F/70	0	0	1	1	543	557	2.82	2.35	2.35	2.63	10	10	timolol
F/53	0	0	1	1	565	564	1.79	2.02	1.58	1.18	16	18	betaxolol
F/54	2	2	1	1	570	564	1.82	1.67	1.67	1.71	18	16	betaxolol
F/68	0	0	1	1	570	570	1.75	2.14	1.30	1.07	11	11	timolol
F/70	1.5	1.5	1	1	561	550	1.36	2.31	0.93	1.02	17	17	carteolol
F/59	-2	-3	1	1	559	560	1.65	1.62	2.28	2.31	13	14	betaxolol
F/57	1	1	1	1	535	534	2.24	2.62	2.63	2.42	16	17	betaxolol
F/65	-5	-5	1	1	562	567	1.74	4.63	1.57	1.75	15	15	vistagan
F/64	2	2	1	1	544	544	2.76	1.85	1.55	1.34	16	17	timolol
M/60	0	0	1	1	567	581	20.00	22.95	21.00	22.14	12	12	timolol
M/53	0	0	1	1	550	550	1.01	1.44	1.57	1.46	14	14	carteolol
M/56	1	1	1	1	578	570	1.65	1.99	1.75	1.99	15	16	carteolol
M/66	0	0	1	1	540	540	2.51	1.75	3.11	1.59	10	13	timolol
M/50	-3.5	-3.5	1	1	542	543	18.32	4.97	18.27	4.70	15	15	timolol
M/52	0	0	1	1	539	538	1.71	1.54	1.98	1.76	15	15	betaxolol
M/69	0	0	1	1	539	548	2.62	1.66	2.65	1.70	15	12	timolol
M/60	1	1	1	1	570	565	1.21	1.69	1.33	1.48	18	17	carteolol
M/70	1	1	1	1	560	570	2.03	3.08	1.74	1.83	10	11	carteolol
M/69	0	0	1	1	550	550	2.41	1.72	1.60	1.71	14	14	timolol
M/69	0	0	1	1	551	552	1.98	2.60	0.87	1.92	19	19	betaxolol
M/62	2	2	1	1	580	580	2.38	3.28	3.18	3.41	14	13	betaxolol

Table 1: SC values in the control group.

gender/age	Refraction		Visual acuity		CCT um		VF PD 2005		VF PD 2012		IOP		Therapy
	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	
F/62	1.5	-0.5	1	1	550	550	1.49	1.69	1.53	1.66	18	15	latanoprost
F/50	1	0.75	1	1	530	530	3.31	7.71	2.72	2.52	15	16	latanoprost
F/61	-2.5	-2.25	1	1	580	580	1.93	1.83	2.06	2.02	19	19	latanoprost
F/56	0	0	1	1	524	534	1.68	1.62	1.74	1.34	12	12	bimatoprost
F/50	-4	-4	1	1	530	526	1.95	1.73	2.03	2.18	11	11	bimatoprost
F/69	2	2	1	1	580	580	2.34	1.32	1.99	2.5	13	14	latanoprost
F/61	0	0	1	1	550	560	2.54	2.76	2.17	2.73	19	18	bimatoprost
F/57	0	-1.5	1	1	580	580	2.18	2.13	2.12	1.53	16	15	latanoprost
F/62	0.75	0.75	1	1	539	545	2.86	2.38	2.86	3.26	16	16	latanoprost
F/53	-1	-1	1	1	547	547	1.3	1.8	1.77	2.03	14	14	bimatoprost
F/70	1	1	1	1	564	565	2.85	3.76	2.52	2.53	16	16	latanoprost
F/59	1	1	1	1	570	570	2.56	2.9	2.16	2.19	16	17	bimatoprost
F/59	1	1	1	1	557	555	2.09	2.51	1.85	1.87	15	15	latanoprost
F/52	1	1	1	1	545	555	2.31	2.14	1.88	1.64	14	14	bimatoprost
F/60	-2.5	-2.5	1	1	580	585	1.74	1.65	1.45	1.21	18	20	latanoprost
M/69	1	1	1	1	558	549	2.89	11.78	1.62	4.88	16	16	latanoprost
M/68	-2.5	-1	1	1	568	570	0.88	1.31	0.82	1.29	20	18	latanoprost
M/70	4	4	1	1	579	580	3.22	1.98	3.09	2.39	16	16	bimatoprost
M/68	-2.5	-1	1	1	568	570	0.88	1.31	0.82	1.29	20	19	latanoprost
M/67	2.5	3.5	1	1	551	561	2.37	1.85	1.99	2.04	13	13	latanoprost
M/65	1.25	1.25	1	1	573	574	0.97	2.27	2	2.1	17	17	latanoprost
M/63	2	2	1	1	560	555	11	3.14	6.33	2.78	10	11	latanoprost
M/65	1	1	1	1	520	520	3.13	5.31	2.28	2.08	12	12	latanoprost
M/65	1	1	1	1	580	580	1.69	2.15	1.92	2.69	13	13	bimatoprost
M/67	1	1	1	1	571	580	2.27	2.42	1.02	1.69	16	16	bimatoprost
M/56	-5	-5	1	1	530	525	1.7	2.24	1.76	1.9	14	15	latanoprost
M/50	-2.5	-2.5	1	1	540	540	2.82	2.56	1.82	2.5	15	17	bimatoprost
M/57	1.5	1.5	1	1	570	578	1.61	1.31	2.2	1.69	10	10	latanoprost
M/63	0.75	0.75	1	1	580	580	2.37	5.07	2.94	3.85	18	17	latanoprost
M/61	-5	-5	1	1	520	520	3.37	3.77	3.27	4	13	13	bimatoprost

Table 2: SC values in glaucoma eyes.

parameters of the groups treated by timolol, carteolol, betaxozol and vistagan in the β -blockers therapy differs. The value of the parameter PD VF 2005 RE ($p = 0.0436$) being near the evidence value, is probably coincidental. It is also confirmed by the inconclusive value of the left eye parameter of the same parameter VF PD 2005 LE ($p=0.4959$) (Table 4).

For comparison of two treatments - bimatoprost and latanoprost in the treatment with prostaglandins, the nonparametric two-sided Mann-Whitney's test was used again because of large remoteness of some measurements and therefore abnormal data. The test assesses whether the medians differ within both groups. The statistical analysis of Mann-Whitney's test shows that the groups treated with the latanoprost and bimatoprost do not differ in any of the observed parameters (Table 5).

Discussion

Vasudeana et al. [7] ensues that both β -blockers and prostaglandins have, besides reducing IOP, a neuroprotective effect on RGC.

Mesmer et al. [8] observed visual fields prior to administration of 0.5% timolol or 0.5% betaxolol, and following that at intervals of 3, 6, 12 and 18 months. They have found that the visual fields tended to improve during the first six months of treatment and remained stable or tended to deteriorate thereafter. The treatment effect on the visual field was better in the betaxolol-treated group than it was in the timolol-treated group ($P=0.041$).

In a prospective, randomized, double-masked study, 44 patients with primary open-angle glaucoma were treated either with 0.5% betaxolol or 0.5% timolol in both eyes twice a day. Twenty-nine patients could be followed up for 48 months. Seventeen of these patients were treated with betaxolol and 12 with timolol. However, the visual fields improved more in the betaxolol group. Patients treated with betaxolol had significantly smaller mean defects ($p < 0.05$) and higher mean sensitivities ($p < 0.05$, Wilcoxon rank score test) than did the timolol-treated patients in months 3, 6, 12, and 18 [9].

Drance [10] compared the effect of betaxolol, timolol, and pilocarpine on visual functions by means of short-wave automated perimetry in patients with glaucoma in the course of 24 months. There were no significant differences between the drug effects on the visual fields.

Similar results were obtained by Vainio et al. [11] who examined visual fields of sixty-four glaucoma patients treated with either 0.5% betaxolol or 0.25% timolol eye drops twice a day. The Octopus visual field performance was followed up for 2 years and analyzed to find diffuse and localized changes. There was no statistically significant difference between betaxolol and timolol treated patients either in the change in mean retinal sensitivity or in the change in localized scotomatous areas.

Even the study by Arai et al. [12] presents similar findings. This study, which lasted two years and compared the results of treatment with betaxolol and timolol, concluded that the mean deviation and

Parameters	P
Age	0.347
CCT RE	0.584
CCT LE	0.442
PD RE 2005	0.604
PD LE 2005	0.773
PD RE 2012	0.836
PD LE 2012	0.395
IOP RE	0.395
IOP LE	0.520

Table 3: Mann-Whitney's test assessing single parameters.

Visual field	P
PD RE 2005	0.0436
PD LE 2005	0.4959
PD RE 2012	0.5502
PD LE 2012	0.5762

Table 4: P values for PD in the treatment with β -blockers.

Visual field	P
PD RE 2005	0.6669
PD LE 2005	0.8972
PD RE 2012	0.9656
PD LE 2012	0.5758

Table 5: P values for PD in the treatment with prostaglandin.

corrected pattern standard deviation showed no significant change in either group.

Our results are in line with most of the above cited studies. Over the course of 7 years, we found no differences in evaluated parameters (CCT, PD, IOP) when comparing treatment with β -blockers and prostaglandins.

Studies comparing the visual field in glaucoma patients treated with β -blockers and prostaglandins are yet to be published. Pajic et al. [13] reported the results of following up the visual fields in patients treated with a fixed combination of dorzolamid/timolol and latanoprost/timolol, and found that treatment with the dorzolamid/timolol fixed combination seemed to be effective in preventing glaucomatous visual field progression.

To eliminate the influence of age, gender, CCT, and various changes in the visual field, we set up approximately similar homogeneous groups. A greater progression of changes in visual fields was seen in thin corneas [14]. We know that testing the visual field with a visual field analyzer is not the most sensitive functional examination for glaucoma of the visual analyzer. Kerrigen-Baumrid [15] proved that at least 25% to 35% RGC loss is associated with statistical abnormalities in automated visual field testing. Nevertheless, we consider the application of this method for assessment of the state of the visual pathway as appropriate.

Conclusion

There does not seem to be a significant difference in VF between glaucoma patients treated with β -blockers and PG monotherapy.

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