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Comparison of latanoprost, brimonidine tartrate, and bimatoprost plus timolol maleate in fixed combinations

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Aim: To compare the intraocular pressure (IOP)-lowering efficacy of fixed-combination antiglaucoma agents, and to evaluate the effect of these drugs on the visual field and optic disk morphology.

Materials and methods: Included in this retrospective study were 17 eyes receiving latanoprost 0.005% + timolol maleate 0.5% fixed combination (group 1), 18 eyes receiving brimonidine tartrate 0.2% + timolol maleate 0.5% fixed combination (group 2), and 16 eyes receiving bimatoprost 0.03% + timolol maleate 0.5% fixed combination (group 3), all with the diagnosis of primary open-angle glaucoma or ocular hypertension. Intraocular pressure was measured by Goldmann applanation tonometer, a visual field test was performed, and optic disk morphology was evaluated by optic coherence tomography before the initiation of treatment and at the end of the follow-up period. The results were compared statistically.

Results: All 3 fixed-combination drugs reduced IOP significantly compared to the baseline (for all groups, $P < 0.001$), although it was more pronounced in the group receiving the bimatoprost 0.03% + timolol maleate 0.5% fixed combination. No significant change was seen in the visual field and optic disk morphology in any group.

Conclusion: All 3 fixed combinations are effective in lowering IOP and preserving the visual field and optic disk morphology.

Key words: Bimatoprost, brimonidine tartrate, glaucoma, latanoprost

1. Introduction

Primary open-angle glaucoma is a chronic progressive optic neuropathy, characterized by retinal ganglion cell loss that can cause visual field defects and severe visual loss. The prevalence of primary open-angle glaucoma is estimated to be 1%–8% worldwide (1,2). Elevated intraocular pressure (IOP) is believed to be the main risk factor for glaucomatous damage and topical medications are the mainstay of glaucoma therapy. The goal of treatment is to reduce the IOP to a level that prevents progressive visual loss. If monotherapy is not sufficient to reach the target IOP, medication can be changed or an adjunctive topical agent can be added. If a second medication is planned to be added, a fixed-combination drug may be preferred to increase patient compliance. Additionally, exposure to ocular preservatives and drug washout, which can happen if 2 or more drugs are used, can be avoided. The European Glaucoma Society suggests using fixed-combination drugs in place of 2 separate instillations of the same agents whenever possible (3).

In this study, we aimed to compare the IOP-lowering efficacy of fixed combinations of latanoprost 0.005% + timolol maleate 0.5%, brimonidine tartrate 0.2% + timolol maleate 0.5%, and bimatoprost 0.03% + timolol maleate 0.5%, and to evaluate the effect of these fixed combinations on the visual field and optic disk morphology.

2. Materials and methods

This study was performed retrospectively and subjects with early primary open-angle glaucoma or ocular hypertension whose IOP was controlled using fixed combinations of latanoprost 0.005% + timolol maleate 0.5% (Xalacom, Pfizer, Turkey), brimonidine tartrate 0.2% + timolol maleate 0.5% (Combigan, Abdi İbrahim, Turkey), or bimatoprost 0.03% + timolol maleate 0.5% (Ganfort, Abdi İbrahim) were enrolled in the study. Early primary open-angle glaucoma was diagnosed as an elevated IOP (≥21 mmHg by a Goldmann applanation tonometer), open angle on gonioscopy, glaucomatous cupping on funduscopic examination with a 90 diopter lens at the slit-

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lamp, and characteristic visual field defects on central 24-2 threshold Humphrey visual field test and mean deviation between −5.0 and −10.0 dB. Ocular hypertension was defined as elevated IOP without clinically relevant visual field loss and optic nerve head changes. The right eye was included in subjects with bilateral cases. Subjects having any ocular disease like corneal opacities or any kind and grade of lens opacification that could affect IOP measurement, visual field test, or optic disk tomography (OCT) measurement; visual acuity lower than 20/30; any systemic disorder or medication known to influence visual function; or a history of eye trauma were excluded from the study. Subjects were divided into 3 groups. Group 1 consisted of 17 eyes receiving latanoprost 0.005% + timolol maleate 0.5% fixed combination, group 2 consisted of 18 eyes receiving brimonidine tartrate 0.2% + timolol maleate 0.5% fixed combination, and group 3 consisted of 16 eyes receiving bimatoprost 0.03% + timolol maleate 0.5% fixed combination.

IOP was measured using a Goldmann applanation tonometer. Visual field testing was performed twice using the Humphrey visual field analyzer full-threshold strategy 24-2, and the more reliable test was included in the study. Visual field tests with fixation loss, false-positive errors, and/or false-negative errors of less than 33% were determined to be reliable. Mean deviation (MD), short term fluctuation (SF), pattern standard deviation (PSD), and corrected pattern standard deviation (CPSD) were recorded. Optic nerve head morphology and peripapillary nerve fiber layer examination was performed using spectral domain OCT (Cirrus HD-OCT Model 4000, Carl Zeiss Meditec, Dublin, CA, USA). Scan protocol was an optic disk cube of 200 × 200. We analyzed the overall average retinal nerve fiber layer (RNFL) thickness (μm) in superior, temporal, inferior, and nasal quadrants. Rim area (mm^2), disk area (mm^2), average cup/disk (C/D) ratio, vertical C/D ratio, and cup volume (mm^3) were recorded. Image quality (signal strength) was 6 or more on a 0–10 scale in all subjects. Examinations were performed before the initiation of antiglaucoma drugs and at the end of the follow-up period.

The difference in age, follow-up time, and mean IOP change among groups was evaluated by the Kruskal–Wallis H test. If a significant difference was found, the change was compared between groups using the Mann–Whitney U test. Sex distribution was evaluated by a chi-square test. The change in IOP, visual field test, and OCT test parameters at first visit and at the end of the follow-up was compared using Wilcoxon signed ranks test. For all tests, P values lower than 0.05 were determined to be significant.

3. Results

The mean age was 65.71 ± 10.2 years in group 1, 56.56 ± 12.4 years in group 2, and 57.19 ± 14.3 years in group 3 (P = 0.044). The mean age was significantly higher in group 1 compared to group 2, whereas there was no significant difference between group 1 and group 3 (P = 0.019 and P = 0.053, respectively). The mean age did not differ between group 2 and group 3 (P = 0.93). In group 1, 9 subjects were female and 8 subjects were male; in group 2, 9 subjects were female and 9 subjects were male; in group 3, 9 subjects were female and 7 subjects were male (P = 0.94). Follow-up time was 11.3 ± 4.5 months (6–18 months) for group 1, 9.9 ± 3.2 months (4–18 months) for group 2, and 6.8 ± 1.9 months (4–10 months) for group 3 (P = 0.002).

The fixed combinations of latanoprost 0.005% + timolol maleate 0.5%, brimonidine tartrate 0.2% + timolol maleate 0.5%, and bimatoprost 0.03% + timolol maleate 0.5% all reduced IOP efficiently as compared with the baseline (Table 1) and the mean reduction in IOP from the baseline was 6.8 ± 2.5 mmHg, 6.7 ± 2.8 mmHg, and 10.6 ± 3.4 mmHg, respectively (P = 0.002). IOP decreased by 32.1% in group 1, 30.2% in group 2, and 42.2% in group 3. The mean IOP reduction rate was higher in group 3 compared to group 1 and group 2, whereas there was no significant difference between group 1 and group 2 (P = 0.002, P = 0.001, and P = 0.73, respectively).

Table 1. Intraocular pressure change in groups.

Group (fixed combination)	Pretreatment IOP (mmHg)	Posttreatment IOP (mmHg)	P value
Group 1	21.24 ± 2.4	14.47 ± 3.1	<0.001
Group 2	21.89 ± 3.4	15.17 ± 2.7	<0.001
Group 3	24.81 ± 4.2	14.19 ± 2.2	<0.001

Group 1: group receiving latanoprost 0.005% + timolol maleate 0.5% fixed combination; Group 2: group receiving brimonidine tartrate 0.2% + timolol maleate 0.5% fixed combination; Group 3: group receiving bimatoprost 0.03% + timolol maleate 0.5% fixed combination.

Visual field MD, PSD, SF, and CPSD did not differ among groups before treatment (P = 0.08, P = 0.15, P = 0.55, and P = 0.41, respectively). The changes in visual field MD, PSD, CPSD, and SF are given in Table 2. Visual fields did not show any change during treatment in either group.

Optic coherence tomography parameters did not show any significant change among groups before treatment. The P value was 0.26 for overall average RNFL, 0.70 for RNFL in the superior quadrant, 0.97 for RNFL in the temporal quadrant, 0.11 for RNFL in the inferior quadrant, 0.07 for RNFL in the nasal quadrant, 0.67 for the rim area, 0.18 for the disk area, 0.44 for the average cup/disk ratio, 0.20 for the vertical C/D ratio, and 0.79 for the cup volume. The OCT parameters measured at the beginning and at last visit in all groups are given in Tables 3 and 4. Optic disk morphology did not show a

Table 2. Visual field parameters in treatment groups.

Visual field test parameter		Group 1	Group 2	Group 3
MD	Pretreatment	−2.67 ± 2.0	−3.93 ± 2.3	−4.59 ± 2.2
	Posttreatment	−2.43 ± 2.5	−3.86 ± 2.3	−4.51 ± 3.0
	P	0.25	0.54	0.26
PSD	Pretreatment	2.81 ± 0.8	3.66 ± 2.3	2.94 ± 2.1
	Posttreatment	2.69 ± 1.1	2.98 ± 1.4	2.80 ± 1.8
	P	0.25	0.38	0.15
CPSD	Pretreatment	1.46 ± 1.3	2.21 ± 2.3	1.75 ± 2.5
	Posttreatment	1.45 ± 1.0	1.74 ± 1.7	1.66 ± 2.2
	P	0.69	0.43	0.58
SF	Pretreatment	2.11 ± 0.9	2.55 ± 1.3	1.98 ± 0.6
	Posttreatment	2.01 ± 1.0	2.17 ± 1.0	1.77 ± 0.4
	P	0.40	0.99	0.16

Group 1: group receiving latanoprost 0.005% + timolol maleate 0.5% fixed combination; Group 2: group receiving brimonidine tartrate 0.2% + timolol maleate 0.5% fixed combination; Group 3: group receiving bimatoprost 0.03% + timolol maleate 0.5% fixed combination; MD: mean deviation; PSD: pattern standard deviation; CPSD: corrected pattern standard deviation; SF: short-term fluctuation; P: Wilcoxon signed ranks test.

Table 3. Optic coherence tomography parameters.

Parameter		Group 1	Group 2	Group 3
Average RNFL (μm)	Pretreatment	84.47 ± 12.1	87.53 ± 9.8	90.22 ± 9.5
	Posttreatment	83.57 ± 13.9	86.53 ± 11.7	89.57 ± 11.0
	P	0.25	0.89	0.89
RNFL superior (μm)	Pretreatment	106.65 ± 23.0	108.07 ± 14.1	110.61 ± 16.9
	Posttreatment	108.79 ± 26.5	105.00 ± 13.1	103.43 ± 25.3
	P	0.29	0.20	0.07
RNFL temporal (μm)	Pretreatment	61.82 ± 8.8	61.73 ± 11.9	61.39 ± 11.9
	Posttreatment	65.00 ± 11.5	61.67 ± 12.9	64.5 ± 15.6
	P	0.92	0.78	0.67
RNFL inferior (μm)	Pretreatment	106.00 ± 20.1	114.73 ± 16.9	116.33 ± 16.3
	Posttreatment	99.14 ± 27.7	116.27 ± 20.9	117.21 ± 12.9
	P	0.25	0.46	0.53
RNFL nasal (μm)	Pretreatment	63.59 ± 5.9	65.47 ± 14.4	72.28 ± 12.5
	Posttreatment	60.79 ± 6.9	63.53 ± 14.0	72.36 ± 23.4
	P	0.11	0.64	0.97

Group 1: group receiving latanoprost 0.005% + timolol maleate 0.5% fixed combination; Group 2: group receiving brimonidine tartrate 0.2% + timolol maleate 0.5% fixed combination; Group 3: group receiving bimatoprost 0.03% + timolol maleate 0.5% fixed combination; RNFL: retinal nerve fiber layer; P: Wilcoxon signed ranks test.

Table 4. Optic coherence tomography parameters.

Parameter		Group 1	Group 2	Group 3
Rim area (mm^2)	Pretreatment	1.22 ± 0.3	1.21 ± 0.1	1.27 ± 0.3
	Posttreatment	1.19 ± 0.3	1.16 ± 0.2	1.34 ± 0.6
	P	0.08	0,07	0.94
Disk area (mm^2)	Pretreatment	2.22 ± 0.4	1.98 ± 0.5	2.24 ± 0.4
	Posttreatment	2.25 ± 0.6	1.91 ± 0.4	2.33 ± 0.6
	P	0.73	0,07	0.38
Average C/D ratio	Pretreatment	0.63 ± 0.1	0.56 ± 0.2	0.63 ± 0.1
	Posttreatment	0.62 ± 0.2	0.58 ± 0.2	0.63 ± 0.1
	P	0.97	0.28	0.56
Vertical C/D ratio	Pretreatment	0.60 ± 0.1	0.52 ± 0.2	0.62 ± 0.8
	Posttreatment	0.56 ± 0.2	0.54 ± 0.2	0.63 ± 0.1
	P	0.62	0,07	0.92
Cup volume (mm^3)	Pretreatment	0.30 ± 0.2	0.25 ± 0.2	0.31 ± 0.2
	Posttreatment	0.35 ± 0.2	0.27 ± 0.2	0.33 ± 0.2
	P	0.18	0.51	0.18

Group 1: group receiving latanoprost 0.005% + timolol maleate 0.5% fixed combination; Group 2: group receiving brimonidine tartrate 0.2% + timolol maleate 0.5% fixed combination; Group 3: group receiving bimatoprost 0.03% + timolol maleate 0.5% fixed combination; C/D: cup/disk; P: Wilcoxon signed ranks test.

significant change during treatment in the treatment groups.

4. Discussion

Fixed-combination glaucoma drugs have the combined efficacy of 2 ocular hypotensive drugs in a single container, which can aid patient adherence to treatment. In the literature, fixed combinations have been reported to decrease IOP effectively (4–6). In our study, fixed combinations of latanoprost 0.005% + timolol maleate 0.5%, brimonidine tartrate 0.2% + timolol maleate 0.5%, and bimatoprost 0.03% + timolol maleate 0.5% decreased IOP effectively. As bimatoprost 0.03% + timolol maleate 0.5% is the newest fixed combination including prostaglandin analogs, our follow-up time was shorter in group 3 compared to group 1 and group 2. The mean reduction rate in IOP was more pronounced in group 3 (10.6 mmHg) compared to group 1 (6.8 mmHg) or group 2 (6.7 mmHg), whereas the reduction rate in IOP was similar between group 1 and group 2. Although the IOP-lowering efficacy was more pronounced in group 3, it should not be forgotten that the baseline IOP was higher in this group and it is known that starting from a higher baseline IOP may result in higher pressure-reducing efficacy of antiglaucoma medications. Schwenn et al. (4) found the mean IOP reduction value with latanoprost 0.005% + timolol maleate 0.5% fixed combination to be 4.0 mmHg (the IOP lowering rate was 19.7%). Brimonidine tartrate 0.2% + timolol maleate 0.5% fixed combination has been reported to decrease IOP by a mean of 3.9 mmHg from baseline (7). Nixon et al. (8) reported that the brimonidine/timolol fixed combination decreased IOP by a mean of 32.3% from baseline at 3 months, which is in accordance with our results. Similarly to our results, bimatoprost 0.03% + timolol maleate 0.5% fixed combination has been found to have a higher performance than latanoprost 0.005% + timolol maleate 0.5% fixed combination in terms of IOP reduction (5). The mean IOP reduction value with bimatoprost 0.03% + timolol maleate 0.5% fixed combination has been reported to be 13.4 mmHg and the IOP lowering rate to be 45.8% (9). Similarly, our results indicated that the IOP lowering rate of bimatoprost 0.003% + timolol maleate 0.5% fixed combination is 42.2%.

Few reports have assessed the effect of fixed-combination antiglaucoma drugs on the visual field. In the literature, the visual field has been reported to remain stable in subjects receiving latanoprost 0.005% + timolol maleate 0.5% fixed combination (10). Schwenn et al. (4) could not find a significant difference between mean deviation values obtained at baseline and after 24 months of administration of latanoprost 0.005% + timolol maleate 0.5% fixed combination. We could not

find any study about the effect of fixed combinations of brimonidine/timolol or bimatoprost 0.03% + timolol maleate 0.5% on visual field progression. We found that all 3 fixed combinations were effective in preventing progression of glaucomatous visual field damage. There was no change in MD, PSD, SF, or CPSD in treatment groups compared to the baseline. Each 1 mmHg rise in IOP during a median follow-up time of 5.3 years has been shown to be associated with a 19% increased risk of visual field progression (11). This can explain why we observed no change in visual fields in the study groups. Nevertheless, progression of visual field disorder in glaucoma is usually slow. Therefore, long-term follow-up is needed to evaluate the effects of fixed combinations on the preservation of the visual field.

In subjects with early glaucoma, evaluation of the retinal nerve fiber layer is important for evaluating glaucomatous ganglion cell loss. Kanamori et al. (12) showed that the retinal nerve fiber layer decreased in glaucomatous eyes, with or without early visual field defects. In our study, optic disk morphology did not show a significant change in the treatment groups. Spectralis OCT has been reported to have a higher specificity compared to the Heidelberg Retinal Tomograph (HRT) in the diagnosis of glaucoma (13,14). Although we could not find any articles about the change in optic disk morphology using OCT in subjects using fixed combinations, there are some reports using the HRT or scanning laser polarimetry. The HRT revealed optic disk changes in 14.3% of subjects using latanoprost/timolol, which was not statistically significant after logistic regression analysis (4).

Although our study is limited by its retrospective design, our results show that fixed combinations of latanoprost 0.005% + timolol maleate 0.5%, brimonidine tartrate 0.2% + timolol maleate 0.5%, and bimatoprost 0.03% + timolol maleate 0.5% have an efficient IOP-lowering effect, and this effect seems to be more pronounced with bimatoprost 0.03% + timolol maleate 0.5%. All 3 fixed combinations seem to be similarly effective in preventing glaucomatous visual field damage and in protecting optic disk morphology. The effects of fixed combinations on visual field and optic disk morphology need to be evaluated for long-term follow-up in prospective series.

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