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A Short-term Study of the Additive Effect of Latanoprost 0.005% and Brimonidine 0.2%

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Purpose: To evaluate the short-term additive effects of latanoprost 0.005% and brimonidine 0.2%.

Methods: This study was a randomized, double-masked, cross-over study that included 32 patients (32 eyes) with primary open-angle glaucoma or exfoliation glaucoma. On baseline day, intraocular pressure (IOP) was measured at 10 AM and 11 PM. Baseline IOP values were obtained by calculating the mean values for both eyes. After this process, latanoprost 0.005% was prescribed once a day during the first 5 days at 10 PM as the first test drug. During the second 5 days, twice a day brimonidine 0.2% or a placebo, as the second test drug, was added to the latanoprost at 9 AM and 10 PM. After a 4-week washout period, latanoprost 0.005% was prescribed once a day during the first 5 days at 10 PM and during the second 5 days, the second test drug, brimonidine or a placebo, was added to latanoprost, and the two drugs were prescribed twice a day for 5 days.

Results: During the second 5 days, although an additional 2.53–3.10 mm Hg decrease in IOP was determined in the latanoprost + brimonidine group, there was no additional decrease in the latanoprost + placebo group.

Conclusions: This study showed that brimonidine and latanoprost have an additive IOP-lowering effect in open-angle glaucoma patients in the short term. **Jpn J Ophthalmol 2003;47:473–478** © 2003 Japanese Ophthalmological Society

Key Words: Glaucoma, latanoprost, brimonidine.

Introduction

Topical β-adrenergic blockers over the past two decades have been the most commonly prescribed class of medicine to reduce intraocular pressure (IOP) in patients with primary open-angle glaucoma (POAG) or ocular hypertension.[1] However, several years ago two new products became available commercially that have become commonly used ocular hypotensive agents. Latanoprost, a prostaglandin $F_{2\alpha}$ analogue, has proved to be an effective ocular hypotensive drug. Its main mechanism for reducing IOP is an increase in the uveoscleral outflow.[2–5] In long-term studies, latanoprost 0.005%, when applied once daily, reduces IOP at least as effectively as timolol 0.5% applied twice daily or other antiglaucoma agents such as dorzolamide, brimonidine, and other β-blockers).[2,6–9]

Brimonidine tartrate 0.2%, a highly selective α_2-adrenergic agonist, functions by decreasing aqueous humor production and increasing uveoscleral outflow while reducing aqueous humor inflow.[10] In dose–response studies, brimonidine 0.2% twice daily has been found to safely and effectively lower IOP in patients with open-angle glaucoma or ocular hypertension.[11] Topically applied twice daily for 12 months, brimonidine tartrate 0.2% was safe and effective in lowering IOP in patients with glaucoma or ocular hypertension.[12] Brimonidine, when added to existing glaucoma regimens, was safe and effective adjunctive therapy for lowering IOP.[13]

Although it is known that the maximal IOP reducing effect of latanoprost will occur in a longer period, the main purpose of our study was to investigate the additive effects of latanoprost 0.005% and brimonidine 0.2% in a short time period, for use when faster IOP reduction is required. We believe that our study can also indicate the long-term additive effects of these drugs.

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Materials and Methods

This study was designed as a randomized, double-masked trial. It included 32 consecutive patients (32 eyes) who met the following inclusion criteria: 18 years of age or older, have POAG or exfoliation glaucoma with an IOP of at least 22 mm Hg without any previous treatment in the study eye, must not have any previous pharmacological therapy, and with a best corrected visual acuity of 20/200 or better in the study eye. We included only 1 eye of each patient in this study, selecting the eye that had the higher IOP value.

Exclusion criteria included any condition preventing reliable applanation tonometry in the study eye, opacity or patient uncooperativeness that restricted adequate examination of the ocular fundus or anterior chamber in the study eye; concurrent keratitis, conjunctivitis, or uveitis; current use of contact lenses, women of childbearing potential not using reliable means of birth control; pregnant or lactating women; clinically significant, serious, or severe medical or psychiatric condition; previous intraocular conventional surgery or laser surgery in the study eye; risk of visual field or visual acuity worsening as a consequence of participation in the trial; any anticipated change in systemic condition; unwillingness to accept the risk of iris color or eyelash changes in this trial. All patients were fully informed about this study and signed informed consent statements before enrollment. This study was approved by the institutional review board of Cumhuriyet University.

During the prestudy visit a medical and ocular history was taken and any concomitant systemic medications were recorded. Diastolic and systolic blood pressure (DBP, SBP) and heart rate (HR) of the patients were measured before starting the study. An eye examination was carried out, including determination of visual acuity, refraction, a slit-lamp examination, ophthalmoscopy; visual field data were recorded with 30-2 full threshold program automated perimetry (Zeiss-Humphrey Systems II 750; Dublin, CA, USA), and IOP measurement with applanation tonometry (Goldman applanation tonometer). All patients were hospitalized during the study period.

On day 0 (baseline day), IOPs were measured at 10 AM and 11 PM. Baseline IOP values were obtained by calculating the mean of 10 AM and 11 PM values for study eyes before giving any treatment. After this process, latanoprost 0.005% (Xalatan; Pharmacia, Uppsala, Sweden) was applied once a day during the first 5 days at 10 PM, as the first test drug. During the second 5 days, brimonidine 0.2% (Alphagan; Allergan, Irvine, CA, USA) or a placebo (Dacrolux, Alcon Cusi, El Masnou, Barcelona, Spain) was added to latanoprost at 9 AM and 10 PM, and IOP measurements were made at 10 AM and 11 PM. At the end of this period, all test drugs were discontinued. After a 4-week washout period, the second baseline IOP values were obtained by calculating the mean of 9 AM and 5 PM values for the study eyes before applying latanoprost. Then latanoprost was applied once a day during the first 5 days at 10 PM. During the second 5 days, the second test drug (brimonidine or placebo) was added to latanoprost twice a day for 5 days. IOP, SBP, DBP, and HR of the patients were measured at 10 AM and 11 PM on days 0, 1, 3, 5, 6, 8 and 10. The mean values were obtained by calculating the mean of the 10 AM and 11 PM measurements.

Double masking of patients and study personnel was achieved by the use of opaque vials as containers for the study drugs and by using coded labeling. Statistical analysis was performed with the statistical package SPSS 8.0 (SPSS, Chicago, IL, USA). The Student *t*-test was used for baseline IOP evaluation and measurements for each treatment period. Critical *p*-values were .05.

Results

The mean age of the patients was 67.39 ± 8.38 years (45–81 years). There were 15 women and 17 men in this study. All the patients were white. The diagnoses were open-angle glaucoma (n = 18) and capsular glaucoma (n = 14).

The mean baseline IOP and the mean reduction of IOP with latanoprost treatment alone and after latanoprost + brimonidine and latanoprost + placebo combinations for each time period and both groups are shown in Table 1, Table 2, and Figure 1. The mean baseline diurnal IOPs for patients receiving latanoprost + brimonidine and latanoprost + placebo were 27.03 ± 3.12 mm Hg and 26.63 ± 3.20 mm Hg, respectively. The difference between the mean baseline IOP for both groups was not statistically significant ($p > .05$). The mean diurnal IOP at 6, 8, and 10 days of treatment was lower in the latanoprost + brimonidine group than in the latanoprost + placebo group ($p < .05$).

The morning IOP measurements and the evening IOP measurements were analyzed separately, and in both groups, mean morning IOP measurements were lower than mean evening IOP measurements. When the mean morning IOP value of latonoprost + brimonidine group was 19.74 ± 5.14 mm Hg, the mean evening IOP measurement was 19.20 ± 4.49 mm Hg. When the mean morning IOP value of latonoprost + placebo group was 20.60 ± 5.14 mm Hg, the mean evening IOP measurement was 20.10 ± 4.82 mm Hg. There were statistically significant differences between the mean morning and evening IOP measurements for both groups. However,

Table 1. Baseline and After Treatment Mean Intraocular Pressure Values (mm Hg ± SD) at Each Day and Time Period

Time*	Baseline	Day 1	Day 3	Day 5	Day 6	Day 8	Day 10
				Latanoprost + Brimonidine			
10 AM	28.03 ± 3.00	20.34 ± 3.63†	20.00 ± 2.72†	18.22 ± 3.79†	15.84 ± 2.59†	15.72 ± 2.92†	15.20 ± 3.00†
11 PM	26.09 ± 3.54	19.31 ± 3.31†	18.84 ± 3.22†	18.25 ± 3.58†	15.47 ± 2.61†	15.72 ± 3.13†	15.31 ± 3.00†
MD	27.03 ± 3.12	19.68 ± 3.25†	19.47 ± 2.90†	18.19 ± 3.59†	15.66 ± 2.39†	15.66 ± 2.79†	15.09 ± 2.58†
				Latanoprost + Placebo			
10 AM	27.75 ± 3.31	20.80 ± 3.32†	19.59 ± 3.63†	18.38 ± 4.69†	18.53 ± 4.52†	18.91 ± 4.14†	19.16 ± 4.32†
11 PM	25.50 ± 3.57	20.13 ± 3.30†	19.16 ± 4.10†	18.56 ± 4.60†	18.81 ± 4.60†	18.84 ± 4.75†	18.78 ± 4.33†
MD	26.63 ± 3.20	20.44 ± 3.08†	19.38 ± 3.73†	18.47 ± 4.53†	18.69 ± 4.47†	18.88 ± 4.38†	18.97 ± 4.23†

*MD: mean diurnal intraocular pressure.
†Significance value $p < .005$ (compared with baseline values). Student *t*-test.

the mean morning and evening IOP differences were approximately 0.5 mm Hg, and these values are not really higher values. The lowering effects of latanoprost were higher at 10 AM. In contrast to latanoprost, the IOP-lowering effects of brimonidine were higher at 11 PM. Concomitant use of brimonidine resulted in a 0.86 mm Hg IOP reduction in the morning and a 0.90 mm Hg IOP reduction in the evening. So, the addition of brimonidine to latanoprost therapy reduces the IOP throughout the day.

When compared with day 0 values, (''day 1'' values (?) or ''baseline'' values (?) there were statistically significant decreases in the diurnal mean IOPs of both groups throughout the first 5 days of latanoprost treatment ($p < .001$). During the second 5 days of combined treatment, while an additional decrease between 2.53 and 3.10 mm Hg was determined in the latanoprost + brimonidine treatment group ($p < .001$), there was no additional decrease with latanoprost + placebo treatment ($p > .05$). After latanoprost + brimonidine or latanoprost + placebo combined therapy, SBP, DBP, and HR values are shown in Table 3. There was no statistically significant difference between these values. We did not see any adverse effects and no patients were excluded from the study.

Discussion

The combination of two drugs or more is common in the treatment of glaucoma. As a rule, a drug that increases outflow, such as latanoprost or pilocarpine, preferably is combined with a drug that reduces inflow, such as β-adrenergic antagonists or carbonic anhydrase inhibitors.[14,15]

Latanoprost is an analogue of an $F_{2\alpha}$ prostaglandin. It is highly selective for the ''F'' protanoid receptor,[16] and indicated for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension who are intolerant of or inadequately responsive to other IOP-lowering medications.[7,17] Latanoprost monotherapy was at least as effective as a fixed combination timolol-pilocarpine twice-daily treatment in reducing mean diurnal IOP in patients not adequately controlled on topical β-adrenergic antagonists.[18] In our study, in the first 5-day periods of both the latanoprost + brimonidine and the latanoprost + placebo groups, when latanoprost was used alone it reduced IOP ranging from 7.35 (27.2%) to 8.84 (32.7%) mm Hg in the latanoprost + brimonidine group and ranging from 6.19 (23.2%) to 8.16 (30.6%) mm Hg in the latanoprost + placebo group. When compared with timolol maleate given daily, latanoprost 0.005% once daily

Table 2. Intraocular pressure Reduction at 1, 3, 5, 6, 8, and 10 Days for Each Time Period and Both Groups (mm Hg)

Time*	Day 1	Day 3	Day 5	Day 6	Day 8	Day 10
			Latanoprost + Brimonidine			
10 AM	7.69 (27.4%)†	8.03 (28.6%)†	9.81 (35.0%)†	12.19 (43.5%)†	12.31 (43.9%)†	12.83 (45.8%)†
11 PM	6.78 (26.0%)†	7.25 (27.8%)†	7.84 (30.1%)†	10.62 (40.7%)†	10.37 (39.7%)†	10.78 (41.3%)†
MD	7.24 (26.8%)†	7.64 (28.3%)†	8.83 (32.7%)†	11.41 (38.5%)†	11.34 (42.0%)†	11.81 (40.0%)†
			Latanoprost + Placebo			
10 AM	6.25 (22.5%)†	8.16 (29.4%)†	9.37 (33.8%)†	9.22 (33.2%)†	8.84 (31.9%)†	8.59 (31.0%)†
11 PM	5.37 (21.1%)†	6.34 (24.9%)†	6.94 (27.2%)†	6.69 (26.2%)†	6.66 (26.1%)†	6.72 (26.4%)†
MD	5.81 (21.8%)†	7.25 (27.2%)†	8.16 (30.6%)†	7.95 (29.9%)†	7.75 (29.1%)†	7.66 (28.8%)†

*MD: mean diurnal intraocular pressure.
†Significane value $p < .005$ (compared with baseline values). Student *t*-test.

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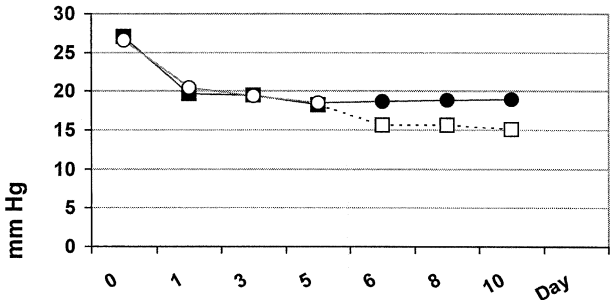

Figure 1. Baseline (day 0) and after treatment mean intraocular pressure values of latanoprost + brimonidine and latanoprost + placebo groups. □: latanoprost + brimonidine, ●: latanoprost + placebo, ■: latanoprost, ○: latanoprost.

has demonstrated either an equal or a statistically greater reduction in intraocular pressure. The efficacy of latanoprost has previously been compared with 0.5% timolol in three 6-month studies. In two of these three studies the IOP reducing effect of latanoprost on diurnal IOP was significantly larger than the effect of timolol.[2,6,7] Toris et al suggested that latanoprost and pilocarpine had an additive effect in their study. Latanoprost and pilocarpine predominantly increased uveoscleral outflow. Whereas pilocarpine increased outflow facility and had no effect on uveoscleral outflow, the additive effect of latanoprost and pilocarpine could be achieved because pilocarpine did not block the uveoscleral outflow induced by latanoprost.[19]

α_2 agonists are a relatively new group of drugs for treatment of glaucoma. Brimonidine tartrate 0.2%, the latest agent in this group, is a relatively selective α_2-adrenergic and an imidazoline receptor agonist. It reduces the IOP primarily by suppressing aqueous formation.[9,20,21] Because of its different chemical structure, brimonidine may have theoretical advantages compared to apraclonidine.[22] The efficacy and safety of brimonidine have been evaluated in previously reported studies. In the Schuman study, brimonidine had a mean IOP-lowering effect which ranged from 6.3 to 7.6 mm Hg. At the 12th hour, the brimonidine group had a mean IOP-lowering effect which ranged from 3.7 to 5.0 mm Hg.[23] Lee and Gornbein[13] reported that after the addition of brimonidine to monotherapy with a nonselective beta blocker the mean additional IOP reduction was 15.5% (3.61 mm Hg), while the addition of brimonidine to latanoprost monotherapy effected a 32.2% (5.89 mm Hg) mean additional IOP reduction. In O'Connor's study,[9] there was a further reduction on IOP with brimonidine when it was added to latanoprost for glaucoma patients. In our study, during the second 5-day period when brimonidine was added to latanoprost (latanoprost + brimonidine group), brimonidine provided an additional lowering effect ranging from 2.53 (14.0%) to 3.10 (17.0%) mm Hg; a 0.86 mm Hg IOP reduction in the morning and a 0.90 mm Hg IOP reduction in the evening. So concomitantly used, brimonidine reduces IOP throughout the day.

In our study, there was no statistically significant additional IOP reduction achieved in the latanoprost + placebo group after addition of the placebo. Brimonidine 0.2% was more effective than betaxolol 0.25% in lowering IOP in patients with open-angle glaucoma or ocular hypertension.[11] Stewart suggested that there was similar efficacy and safety between monotherapy treatment with brimonidine or dorzolamide when each was given three times daily to patients with ocular hypertension or POAG.[24] Brimonidine is safe and effective in the long-term lowering of IOP in patients with POAG or ocular hypertension, with efficacy comparable to that of timolol maleate.[25]

Brimonidine 0.2% may be the most appropriate concentration. It has been shown that brimonidine 0.2% was well tolerated, safe, and clinically effective in lowering IOP in patients with POAG or ocular hypertension. Brimonidine 0.2% instilled twice daily offered long-term IOP control comparable with that achieved with timolol 0.5% and better than with betaxolol 0.25%.[14,26] Clinical studies have been performed for acute indications using the 0.5% concentration of brimonidine, while for chronic indications using the 0.2% concentration.[27] Yüksel et al,[28] Centofanti et al[29] and Arıcı et al[30] suggested that a combination of brimonidine and timolol may have potential in the treatment of glaucoma. Many patients

Table 3. Mean Systolic Blood Pressure (SBP) (mm Hg), Diastolic Blood Pressure (DBP) (mm Hg) and Heart Rate (HR) (beats/min) Values of Latanoprost + Brimonidine and Latanoprost + Placebo Groups

Day	SBP	DBP	HR
	Latanoprost + Brimonidine		
0	122.6 ± 13.3	84.5 ± 7.9	79.3 ± 7.1
1	123.9 ± 15.8	85.2 ± 8.1	77.6 ± 4.9
3	121.3 ± 12.3	83.5 ± 6.9	76.5 ± 4.1
5	122.1 ± 14.9	84.3 ± 7.1	74.3 ± 3.9
6	119.8 ± 12.8	83.1 ± 4.9	75.1 ± 5.9
8	120.1 ± 11.3	82.5 ± 6.1	76.4 ± 4.1
10	117.6 ± 13.5	75.6 ± 7.8	75.2 ± 5.1
	Latanoprost + Placebo		
0	122.9 ± 11.9	87.2 ± 4.9	76.2 ± 4.8
1	123.5 ± 13.6	82.6 ± 6.1	76.8 ± 5.5
3	119.3 ± 12.1	82.4 ± 5.8	75.2 ± 4.8
5	117.7 ± 13.1	84.4 ± 6.2	75.5 ± 5.6
6	119.5 ± 13.9	81.2 ± 5.9	74.5 ± 4.1
8	118.1 ± 11.3	79.8 ± 5.9	75.4 ± 4.1
10	119 ± 11.9	82.7 ± 6.1	73.9 ± 4.1

Significance level $p < .005$. Student t-test.

with ocular hypertension and glaucoma who are treated with topical β-blockers eventually require adjunctive therapy to adequately reduce intraocular pressure.[31] Simmons et al suggested that brimonidine 0.2% twice a day may be a more appropriate choice than latanoprost 0.005% four time a day for adjunctive therapy in patients with glaucoma who require more than one agent to lower IOP.[32]

The cardiopulmonary effects of 0.2% brimonidine were limited to a slight reduction in systolic blood pressure during recovery from exercise at 4 hours after instillation.[33] Brimonidine is well tolerated and has a low rate of allergic response.[17] In our study, there were not any cardiopulmonary or allergic side effects.

The use of latanoprost and brimonidine together in our study obtained a 11.94 (44.2%) mm Hg IOP reduction from baseline IOP in patients with POAG or exfoliation glaucoma in a short-term period. This study showed that brimonidine and latanoprost have additive IOP-lowering effects in glaucoma patients. Concomitantly used brimonidine reduces IOP throughout the day. Additional long-term studies are required to further define this additive effect. The determination of the additive effect of glaucoma medications on lowering IOP will help to define optimum treatment regimens.

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