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Comparison of the Intraocular Pressure Lowering Effect of Latanoprost and Carteolol-pilocarpine Combination in Newly Diagnosed Glaucoma

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Purpose: To evaluate the comparative efficacy of latanoprost monotherapy versus combined carteolol and pilocarpine therapy in patients with newly diagnosed glaucoma.

Methods: Masked randomized prospective trial. This study included 51 patients (64 eyes) with newly diagnosed glaucoma or ocular hypertension. The cases were randomly divided into two treatment groups for administration of latanoprost 0.005% once daily, or of carteolol 2% twice daily and pilocarpine 2% twice daily. Mean diurnal intraocular pressure (IOP) was measured at baseline, week 2, week 4, and month 3 after the beginning of treatment. Changes in mean IOP from baseline to the 3-month visit were determined by an analysis of variance.

Results: Mean diurnal IOP values were 25.1 ± 3.1 mm Hg and 25.5 ± 2.5 mm Hg at baseline in the latanoprost monotherapy group and in the carteolol-plus-pilocarpine group, respectively. Diurnal IOP was significantly decreased from baseline to 3 months in both groups ($P < .001$). At this time point, latanoprost monotherapy had reduced mean diurnal IOP by 7.2 ± 2.5 mm Hg (28.7%) and carteolol plus pilocarpine had reduced mean diurnal IOP by 7.4 ± 2.7 mm Hg (29%). There was no difference between the groups in terms of their IOP reduction effect ($P = .51$). Decreased visual acuity and twilight vision, blurred vision, and headache were more frequent in the carteolol-plus-pilocarpine group than in the latanoprost group ($P < .05$).

Conclusions: We concluded that latanoprost monotherapy was at least as effective as the carteolol-pilocarpine combination therapy in reducing mean diurnal IOP in newly diagnosed glaucoma or ocular hypertension. **Jpn J Ophthalmol 2003;47:72–76** © 2003 Japanese Ophthalmological Society

Key Words: Carteolol-pilocarpine combination therapy, glaucoma, latanoprost monotherapy, medical treatment of glaucoma.

Introduction

Glaucoma is a common disease in the elderly population, affecting over 5% of those older than 75 years.[1] The current treatment of these patients is directed at lowering the intraocular pressure (IOP). The most frequently used drug for glaucoma is a topical β-blocker. However, an amount of this agent sufficient to cause bradycardia or respiratory impairment[2] can be absorbed through the nasopharyngeal mucosa into the systemic circulation.[3] Carteolol has fewer cardiovascular side effects than timolol because of its intrinsic sympathomimetic activity,[4] but that could not be demonstrated in elderly patients and patients with asthma.[5,6] Topical β-blockers alone may not sufficiently lower IOP, necessitating additional medications.[7] Pilocarpine, a cholinergic agonist, is frequently used in many areas of the world as an "add-on" therapy in glaucoma management. However, pilocarpine may cause miosis, myopia, progressive closure of the anterior chamber angle,[8,9] and, occasionally, retinal detachment.

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Among the more recently introduced agents, latanoprost (a prostaglandin $F_{2\alpha}$ analogue) appears to be a highly promising medication because of its comparable or better efficacy compared to timolol.[10–13] The main mechanism of action of latanoprost is to increase the uveoscleral outflow of aqueous humour.[14,15] Currently, use of this agent is increasing gradually as a first-line topical medication alternative to the traditional β-blockers for glaucoma patients.

The aim of this study was to compare the short-term efficacy and reliability of latanoprost monotherapy with the combined therapy of carteolol and pilocarpine in newly diagnosed glaucoma or ocular hypertension patients.

Materials and Methods

The local Medical Ethics Committee gave approval for the study, and all patients included in the study gave informed consent. The study protocol followed the guidelines of the Declaration of Helsinki. This observer-masked randomised prospective clinical trial was carried out between September 2000 and January 2002. The study included 60 white patients (65 eyes) with newly diagnosed glaucoma or ocular hypertension. Nine patients were lost to follow-up and a total of 51 white patients (64 eyes) were evaluated. The cases were randomly divided into two groups and matched according to sex, race, and diagnosis. Twenty-five patients (31 eyes) were randomized to latanoprost 0.005% (Xalatan; Pharmacia, Piscataway, NJ, USA), and 26 patients (33 eyes) were randomized to the carteolol 2% (Carteolol; Chauvin, France) plus pilocarpine 2% (Pilosed; Bilim, Turkey) combination administered separately. Latanoprost 0.005% was applied once daily at 9 PM. Carteolol 2% was instilled twice daily (8 AM and 8 PM), and pilocarpine 2% was also administered twice daily (9 AM and 9 PM). The evening dose of pilocarpine and latanoprost were applied separately with a 15-minute interval.

The patients involved in the study were newly diagnosed as having primary open-angle glaucoma, exfoliative glaucoma, pigmentary glaucoma, or ocular hypertension. Exclusion criteria were closed or barely open anterior chamber angle or a history of acute angle closure, intraocular surgery or argon laser trabeculoplasty within 6 months prior to the study, perforating ocular trauma at any time, severe dry-eye syndrome, use of any ocular medication other than for glaucoma, concomitant medication known to affect IOP, pregnancy and nursing, considering pregnancy, current use of contact lenses, ocular inflammation/infection within the previous 15 months, any condition preventing reliable applanation tonometry, history of asthma or cardiac disease, or inability to adhere to the protocol design.

All patients were followed up for at least 3 months. All examinations were performed by an ophthalmologist masked to the medications used. During the study period, there were four scheduled visits; at baseline, at week 2, week 4, and at month 3 after the beginning of the study. At each visit, medical and ocular history were taken, corrected Snellen visual acuity, slit-lamp examination, fundoscopy, evaluation of conjunctival hyperemia and anterior chamber angle, and measurement of the IOP were carried out. Symptomatology and adverse events of all the patients were recorded at each visit.

The IOP measurements were performed at 10 AM and 4 PM at each visit. The diurnal IOP is defined as the mean value of these two measurements. The IOP was measured with a calibrated Goldmann tonometer after fluorescein strip application under topical anesthesia with oxibuprocaine 0.04%. At each time point, three separate measurements were taken for each eye and the mean of the three measurements was used in the statistical analysis. If both eyes of a patient were studied, the mean IOP of both eyes was used in the analysis.

Statistical Analysis

Demographic characteristics and adverse events were compared with the Fisher exact test and independent-samples *t*-test. IOP changes from the baseline to the 6-month visit were evaluated by an analysis of variance. Any differences showing a P value of less than .05 were considered as statistically significant.

Results

The demographic characteristics of the two treatment groups are presented in Table 1. There is no statistical difference between the groups in respect to age, sex, or diagnosis ($P > .05$).

Three patients in the carteolol-plus-pilocarpine group were withdrawn from the study before the study termination. Two of these patients were withdrawn due to blurred vision and 1 patient because of headache. In the latanoprost group, 1 subject was withdrawn owing to allergic conjunctivitis. Withdrawn patients were excluded from the statistical analysis.

The mean diurnal IOP measurements at each time point in both groups are presented in Table 2. The

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Table 1. Demographic Characteristics of the Study Patients

Characteristics	Latanoprost (n = 25)	Carteolol Plus Pilocarpine (n = 26)
Age (y)	63.44 ± 11.2	61.27 ± 8.65
Range	40–76	38–74
Sex		
Female	13	14
Male	12	12
Glaucoma type (no. of eyes)		
Primary open-angle	22	24
Exfoliative	3	2
Pigmentary	1	1
Ocular hypertension	5	6

percentage of IOP reductions from baseline to 3 months are presented in Table 3. Mean diurnal IOP values were 25.1 ± 3.1 mm Hg and 25.5 ± 2.5 mm Hg at baseline in the latanoprost monotherapy group and in the carteolol-plus-pilocarpine group, respectively. Both latanoprost monotherapy and carteolol-plus-pilocarpine treatment produced statistically significant IOP reduction in comparison with baseline values (Figure 1) ($P < .05$). Latanoprost monotherapy caused a mean diurnal IOP reduction of 7.2 ± 2.5 mm Hg corresponding to 28.7% ($P < .001$), and the combination of carteolol and pilocarpine produced a mean diurnal IOP reduction of 7.4 ± 2.7 mm Hg corresponding to 29% ($P < .001$). On the other hand, there was no difference between the groups according to IOP reduction values ($P = .51$), (Figure 2).

Ocular and systemic adverse events are presented in Table 3. Most of the adverse events were mild. The occurrence of the side effects, including ocular discomfort, blurred vision, decreased visual acuity, decreased twilight vision, and headache, were more

Table 2. Mean Diurnal Intraocular Pressure Values (mm Hg) in Each Group at Each Measurement

Time	Latanoprost (n = 24*)	Carteolol Plus Pilocarpine (n = 23*)
Baseline	25.1 ± 3.1	25.5 ± 2.5
Week 2	17.2 ± 3.2	17.2 ± 2.8
Week 4	18.0 ± 2.9	17.7 ± 3.1
Month 3	17.9 ± 2.7	18.01 ± 2.9

*Withdrawn patients were excluded.

Table 3. Percentage of Intraocular Pressure Reduction From Baseline at Each Visit in Both Groups

Time	Latanoprost (n = 24*)	Carteolol Plus Pilocarpine (n = 23*)
Week 2	31.5%	33.2%
Week 4	28.3%	29.7%
Month 3†	29.0%	28.9%

*Withdrawn patients were excluded.

†There was no statistically significant difference between the groups ($P < .05$).

frequent in the carteolol-plus-pilocarpine group than in the latanoprost group ($P < .01$). There was no statistically significant difference in the occurrence of conjunctival hyperemia, punctate corneal erosions, and dizziness between the two groups ($P > .05$). The total number of the adverse events was significantly higher in the carteolol plus pilocarpine group than in the latanoprost group ($P = .01$) (Figure 3). Serious adverse events were not seen for any patients. No cells or flare in the anterior chamber was reported for any patient during the study. Iris pigmentation or eyelash changes did not occur in any patient.

Discussion

The combination of a β-blocker agent and a parasympathomimetic is included in the treatment protocol for glaucoma. A third drug is also required sometimes. However, the use of multidrugs may result in poor patient compliance.[16] Therefore, initiation and continuation of glaucoma treatment with monotherapy as long as possible is important.

This study was designed to compare the efficacy and reliability between latanoprost and the com-

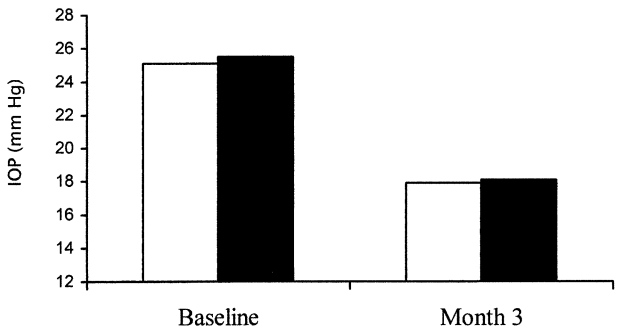

Figure 1. Mean diurnal intraocular pressure (IOP) changes (mm Hg) from baseline to 3 months in both groups. □ Latanoprost, ■ carteolol + pilocarpine.

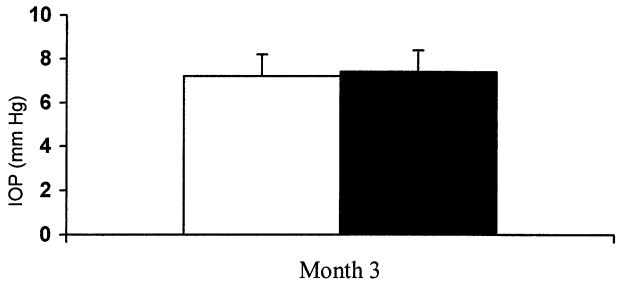

Figure 2. Diurnal intraocular pressure (IOP) reduction values from baseline to 3-month visit in both groups (P = .51). There was no significant difference between the groups. □ Latanoprost, ■ carteolol + pilocarpine.

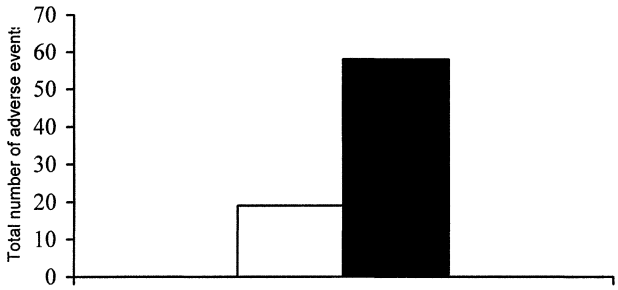

Figure 3. Total number of adverse events during the study period in both groups. Adverse events were significantly more frequent in the carteolol + pilocarpine group (P = .01). □ Latanoprost, ■ carteolol + pilocarpine.

bined cartelolol-plus-pilocarpine treatment in newly diagnosed glaucoma or ocular hypertension patients.

It has been demonstrated that the time of IOP measurement is important because the peak IOP reduction effect of latanoprost is reached 8–12 hours after the drug has been instilled.[17] At the morning measurement, we obtained the peak value for β-blocker and prostaglandin. Because intraocular pressure may fluctuate during the day, we performed the IOP measurements at 13 and 19 hours after the last dose of latanoprost, at 2 and 8 hours after the last dose of carteolol, and at 1 and 7 hours after the last dose of pilocarpine. With two measurements a day, morning and afternoon, we obtained more accurate measurements of the IOP levels.

The results of our study demonstrate that latanoprost 0.005% once daily is at least as effective as carteolol 2% plus pilocarpine 2% twice daily in reducing IOP. Latanoprost reduced mean diurnal IOP by 28.7%, and carteolol plus pilocarpine reduced mean diurnal IOP by 29% by month 3.

Table 4. Ocular and Systemic Adverse Events Reported During the Study

Adverse Event	Latanoprost	Carteolol Plus Pilocarpine
Ocular discomfort	11	19
Blurred vision	1	15
Decreased visual acuity	2	7
Decreased twilight vision	0	5
Conjunctival hyperemia	2	2
Punctate corneal erosions	1	1
Headache	1	8
Dizziness	0	1
Allergic conjunctivitis	1	0
Total	19	58

To our knowledge this is the only study comparing latanoprost with the pilocarpine-plus-carteolol combination. Some studies showed that latanoprost was at least as effective as the timolol plus pilocarpine combination.[18,19] Timolol, as a β-blocker agent without any sympathomimetic activity, may have strong adverse effects in pulmonary diseases, which may restrict timolol use in those patients. Therefore, having intrinsic sympathomimetic activity, carteolol may be superior to timolol for patients having lung problems. Carteolol also is reported to cause less discomfort than timolol.[20] In other respects carteolol shares the general features of β-blockers. For glaucoma cases uncontrolled by β-blockers, switching to latanoprost therapy alone is an alternative way to combination therapy.[18,19]

In the latanoprost monotherapy group, 1 patient was withdrawn from the study while 3 patients were withdrawn from the carteolol-plus-pilocarpine group due to side effects. The occurrence of blurred vision, decreased visual acuity, decreased twilight vision, and headache were significantly less frequent in the latanoprost group than in the combination therapy group. The total number of adverse events was approximately three times higher in the carteolol-plus-pilocarpine group compared to the latanoprost group.

On the Turkish market, latanoprost is three times more expensive than the combined cost of carteolol and pilocarpine. However, the efficacy and the side effects of the two treatment regimens should also be considered. These prices may obviously differ in other countries.

As a result, we concluded that latanoprost monotherapy is at least as effective as the carteolol and pilocarpine combination in reducing mean diurnal IOP in patients with newly diagnosed glaucoma or

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ocular hypertension. Also, latanoprost monotherapy is better tolerated than the carteolol-plus-pilocarpine treatment.

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