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ORIGINAL ARTICLE

Efficacy and Safety of Carteolol Long-acting Solution 2% compared with Timolol Gel-Forming Solution 0.5% in Patients with Primary Open-angle Glaucoma and Ocular Hypertension: A Randomized, Parallel-Group, Open-Label Phase IV Study in Taiwan

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Purpose: The purpose of this study is to compare the efficacy and safety of 2% long-acting carteolol solution with 0.5% timolol gel-forming solution added to primary treatment of 0.005% latanoprost solution in patients with primary open-angle glaucoma and ocular hypertension. **Materials and Methods:** After at least 4 weeks primary treatment with latanoprost, all patients received the combination therapy with either 2% long-acting carteolol or 0.5% timolol gel in addition to latanoprost for 8 weeks. We measured intraocular pressure (IOP) and evaluated systemic and local adverse events between Day 1 and Day 56. **Results:** Carteolol significantly reduced the IOP from baseline (latanoprost monotherapy) by 11.0% at Day 28 and 11.2% at Day 56. Timolol also reduced IOP by 11.5% at Day 28 and 11.0% at Day 56. There was no statistically significant difference in the IOP reduction between the two groups. There was no adverse event related to the administration of these anti-glaucoma medications during the study period. **Conclusions:** Both once daily carteolol and timolol medications are safe and effective treatments combined with latanoprost single therapy.

Key words: Carteolol long-acting solution, timolol gel-forming solution, latanoprost, primary open-angle glaucoma, ocular hypertension

INTRODUCTION

Glaucoma is an ocular disease that causes characteristic optic neuropathy or optic nerve damage, which may result in progressive visual field loss.[1] Elevated intraocular pressure (IOP) is a risk factor for the progression of the optic nerve neuropathy, and lowering IOP by a topical agent, laser or surgical procedure is beneficial to prevent progression of visual field loss in glaucoma. In clinical practice, most patients begin the anti-glaucoma treatments with a single topical drug such as prostaglandin analogs, β-blockers, α-agonists, and carbonic anhydrase inhibitors. However, the IOP reduction effect of single anti-glaucoma medication is not effective in the prevention of glaucomatous optic neuropathy. The causes may be contributed to the tachyphylaxis and long-term drift effects of the drugs. Otherwise, most glaucoma patients need more than one drug to control the IOP throughout their life.

Latanoprost, which stimulates uveoscleral outflow to reduce IOP, is the first-line treatment of primary open-angle glaucoma (POAG) and ocular hypertension (OH), but still some patients achieve insufficient IOP reduction.[2] Concomitant medication by an additional agent with a different mechanism or a fixed combination product is an option to treat these non-responders. Topical β-blockers, such as timolol and carteolol which inhibit aqueous humor production, have also been widely used as twice-daily topical formulations. Once-daily formulations of β-blockers such as 0.5% timolol gel-forming solution (Timoptol® XE) and 2% carteolol alginate formulation (Mikelan® LA) have been available since 1999 and 2002, respectively, with a view of improving adherence to medication and reducing local and systemic adverse events. Fixed combination products containing prostaglandin and timolol have been developed to potentiate the efficacy and to improve adherence. However, prostaglandins and β-blockers are recommended to instill at different time point to achieve maximal IOP-lowering effect: Prostaglandin in the evening and β-blocker in the morning.[3-5] Thus, it seems rational to

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instill both agents separately to maximize the therapeutic outcome.

In this study, we compared the efficacy and safety of combined medication in patients with POAG and OH who are insufficiently controlled by latanoprost monotherapy, using a 0.005% latanoprost at evening in combination with a once-daily dose of either timolol or carteolol medication in the morning, in a randomized, parallel, and open-labeled study.

MATERIALS AND METHODS

This study was designed as a single-center, randomized, parallel-group, and open-label, active-controlled trial carried out at the Department of Ophthalmology, Tri-Service General Hospital in Taiwan. The protocol was reviewed and approved by the institutional review boards, was a registry in ClinicalTrials.gov registration system (NCT00972426), and the study was conducted in accordance with the declaration of Helsinki, good clinical practice, and local regulations. All patients were fully informed and provided written consent before enrollment.

The patients were included in the study if they met all of the following criteria:

1. Male or female outpatients ≥20 years of age with POAG and OH;
2. Subjects who had received latanoprost for at least 4 weeks; and
3. Subjects whose IOP was ≥18 mmHg in at least one eye or whose IOP reduction was judged to be insufficient in the end of screening period.

Exclusion criteria included hypersensitivity to either oral or topical β-blocker or to any ophthalmic solution used in the study, contact lens use, severe dry eye, ophthalmic surgery within 2 or 3 months, ocular infectious or inflammatory disorder within 2 months, herpetic keratitis or corneal ulcer within 2 months, systemic administration of drugs that may have an effect on IOP, poorly controlled cardiovascular diseases, respiratory diseases such as asthma, poorly controlled diabetes, confirmed or potential pregnancy, and current lactation. Patients were screened for enrollment at the first visit, and were treated with only 0.005% latanoprost once daily for at least 4 weeks. At visit 2 (Day 1), eligible subjects were assigned to consecutively to one of the two groups according to prepared randomization schedules. Subjects were treated with 2% long-acting carteolol (CL group) or 0.5% timolol gel (TL group) once daily in the morning combined with treatment with latanoprost in the evening for 8 weeks. All subjects were scheduled to visit between Day 1 and Day 56 for IOP measurement by Goldmann applanation tonometry as the primary outcome and safety assessment of systemic and local adverse events. The safety evaluation included systemic signs such as pulse rate, systolic and diastolic blood pressure (SBP and DBP), and all adverse events that had happened during the clinical trial. For statistical analysis of the IOP differences, *t*-test was used. To examine the noncontinuous variables among two groups, Chi-square test or Fisher's exact test were performed. A $P < 0.05$ was considered to represent a statistically significant difference.

RESULTS

A total of 33 subjects who were diagnosed as POAG and OH with primary treatment with latanoprost single therapy for more than 4 weeks were included in the study. All subjects were randomized in this study, 17 subjects in CL group and 16 subjects in TL group. All subjects completed the study at all visit and the efficacy and safety evaluation. The characteristics of patients at screening and baseline were summarized in Table 1. The mean age of the CL and TL group was 58.7 ± 12.77 years and 48.5 ± 18.73 years, respectively. The IOP at screening of the CL and TL group was 19.8 ± 2.50 mmHg and 20.2 ± 1.88 mmHg, respectively. The IOP at baseline of the CL and TL group was 17.8 ± 2.41 mmHg and 18.6 ± 2.94 mmHg, respectively. There was no statistically significant difference in age and IOP at screening and baseline between the two groups. The result showed that there was no significant difference between the two groups before starting the combination therapy with either carteolol or timolol medication.

For the efficacy evaluation, the IOP of CL group and TL group were measured between Day 1 and Day 56. The results of the selected eyes were listed in Table 2. The mean IOP of CL group was 17.8 ± 2.41 mmHg at baseline

Table 1. Baseline characteristics of subjects enrolled

Study groups	CL group	TL group	*P* value
	n = 17	*n* = 16	
Sex (*n*, %)			
Male	5 (29.4)	6 (37.5)	0.7207
Female	12 (70.6)	10 (62.5)	
Age (years)			
Mean±SD	58.7±12.77	48.5±18.73	0.0755
Median	58.0	53.0	
Range	35–82	20–72	
IOP (mean±SD)			
Screening	19.8±2.50	20.2±1.88	0.6372
Baseline (Day 1)	17.8±2.41	18.6±2.94	0.4346

CL = once daily carteolol plus latanoprost; TL = once daily timolol plus latanoprost; SD = standard deviation; IOP = intraocular pressure

Table 2. Summary of the change of IOP from baseline

Study groups	CL group	TL group	*P* value
	n = 17	*n* = 16	
Baseline (Day 1)			
n	17	16	
Mean±SD (mmHg)	17.8±2.41	18.6±2.94	0.4346
Day 28			
n	17	16	
Mean±SD (mmHg)	15.8±2.24	16.3±2.32	0.8914
Change from baseline			
Mean±SD (mmHg)	−2.0±1.83	−2.3±2.66	0.8870
Intra-*P* value	0.0003	0.00034	
Percentage change from baseline			
Mean±SD (mmHg)	−11.0±9.67	−11.5±11.80	0.8301
Intra-*P* value	0.0003	0.00014	
Day 56			
n	17	16	
Mean±SD (mmHg)	15.7±1.71	16.3±1.98	0.5565
Change from baseline			
Mean±SD (mmHg)	−2.1±1.81	−2.3±2.69	0.5434
Intra-*P* value	0.0002	0.0045	
Percentage change from baseline			
Mean±SD (mmHg)	−11.2±8.86	−11.0±11.75	0.5019
Intra-*P* value	<0.0001	0.0019	

CL = once daily carteolol plus latanoprost; TL = once daily timolol plus latanoprost; SD = standard deviation; IOP = intraocular pressure

and 15.8 ± 2.24 mmHg at Day 28. The mean IOP reduction obtained after 28 days of treatment was 2.0 ± 1.83 mmHg (11.0% reduction). At Day 56, the mean IOP changed to 15.7 ± 1.71 mmHg. The combination treatment of carteolol and latanoprost resulted in IOP reduction of 2.1 ± 1.81 mmHg (11.2% reduction) at Day 56. The mean IOP of TL group was 18.6 ± 2.94 mmHg at baseline and 16.3 ± 2.22 mmHg after 28 days of treatment. The mean IOP reduction obtained at Day 28 was 2.3 ± 2.66 mmHg (11.5%). At Day 56, the mean IOP changed to 16.3 ± 1.98 mmHg. The combination treatment of timolol and latanoprostn resulted in IOP reduction of 2.3 ± 2.69 mmHg (11.0%) at Day 56. There was a significant reduction of IOP from baseline by both combination therapy at Day 28 and Day 56. Neither the mean change nor percent change in IOP in CL group was statistically different from that of TL group at Day 28, and Day 56. According to the study results, the main effect of IOP reduction was similar in the CL and TL groups.

In the aspect of the adverse events, there were only three subjects in TL groups reported adverse events (mild eye irritation in two subjects and mild blurred vision in one subject). However, these adverse events were judged to be unrelated to the study drug. Vital signs were assessed on every visit (data not shown). Subjects in CL group had a statistical significant increase in SBP by 2.7 ± 5.16 mmHg at Day 28 (P = 0.0460), but did not have clinical meaning judged by the investigator. At the end of study, no significant changes of SBP, DBP and pulse rate within each treatment group from baseline were obtained, and there was no significant difference between the two groups.

DISCUSSION

The common anti-glaucoma medications include prostaglandin analogs, β-blockers, α-agonists, cholinergic agonists, carbonic anhydrase inhibitors. The major mechanism of IOP reduction includes 2 parts, one is decreased aqueous production of the ciliary body, and the other one is increased aqueous outflow. Prostaglandin analogs, α-agonists, and cholinergic agonists share the mechanism of increased aqueous outflow, and β-blockers and carbonic anhydrase inhibitors share the mechanism of decreased aqueous production. Prostaglandins, as the strongest anti-glaucoma medication, have IOP-lowering of 20-30% and less side-effects. β-blockers can inhibit cyclic adenosine monophosphate production in ciliary epithelium and lower IOP by 20-30%. Carteolol, a kind of β-blockers, demonstrates intrinsic sympathomimetic activity and has less systemic side effects, such as the bradycardia, heart block, and bronchospasm. The additive effect of β-blockers to miotics, α-agonists, carbonic anhydrase inhibitors, and prostaglandin analogs are well-known. Thus, the combination therapy was proposed to combine 2 different anti-glaucoma medications of different mechanism to achieve maximal IOP reduction effect.[6]

In this study, we evaluated the efficacy and safety of the combination treatment with latanoprost and once daily formulation of carteolol or timolol in the patients previously treated with single therapy of latanoprost. Our results showed the similar efficacy and safety of these combination therapies. The mean decrease in IOP at 8 weeks in CL and TL group was 2.1 (11.2% reduction from baseline) and 2.3 mmHg (11.0%), respectively. In a similar study with patients treated with latanoprost monotherapy for 4 weeks followed by the combination with latanoprost plus timolol gel for 6 weeks, the reduction of IOP was 2.9 mmHg at 6 weeks of combination therapy.[7] In this study, examining the effect of a fixed combination of latanoprost and timolol in patients with insufficient IOP reduction by latanoprost monotherapy, further IOP reduction by the product was 1.8-3.7 mmHg depending on the time point of

IOP measurements.[8] Thus, our present results seem to be consistent with these previous studies on the combination of latanoprost and β-blocker.

Previous reports examining the incident of superficial punctate keratitis (SPK) in patients treated with various topical agents for at least 3 months showed that significant less SPK in patients treated with carteolol than in patients treated with other agents including latanoprost and timolol.[9] In this study, no local adverse event was found after combined medication. This discrepancy may be due to the following reason; in the previous study examining the incidence of SPK after glaucoma medications, dosing period was at least 3 months, and therefore, the study period in the present study was too short to be able to detect any local adverse event and difference in their incidence between the two groups.

Systemic adverse events reported with the use of β-blockers are bradycardia, decrease in SBP and DBP; however, we also failed to find any systemic adverse event in both groups probably because of the same reason described above.

CONCLUSION

The combination therapy of latanoprost and once-daily carteolol or timolol is safe and effective treatment for POAG and OH as an option of ad-on therapy to latanoprost.

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CONFLICT OF INTEREST

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