

Additive intraocular pressure-lowering effect of dorzolamide 1%/timolol 0.5% fixed combination on prostaglandin monotherapy in patients with normal tension glaucoma

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Purpose: To evaluate the intraocular pressure (IOP)-lowering effect of adding dorzolamide 1.0%/timolol 0.5% fixed combination (DTFC) to prostaglandin analogs (PGAs) as monotherapy in patients with normal tension glaucoma.

Methods: A prospective, clinical, case-controlled study of patients with normal tension glaucoma. Patients had been on a once-daily night dose of prostaglandins (PGs) as monotherapy and then received DTFC added to PGs for 8 weeks. The IOP was measured at 9 am, week 0 (baseline), week 4, and week 8.

Results: The baseline IOP of 40 patients who had previously been treated by prostaglandin monotherapy was 15.6 ± 2.0 mmHg at baseline. The IOPs at 4 and 8 weeks after adding DTFC to PGs were 13.5 ± 2.1 mmHg and 13.7 ± 2.2 mmHg, respectively. Significant decrease of the IOP was observed at each time point of measurement as compared with the baseline IOP before adding DTFC ($P = 0.01$). The percent IOP reduction from the baseline IOP at week 4 and week 8 was $13.5\% \pm 12.3\%$ and $11.7\% \pm 13.1\%$, respectively. The percentage of patients who achieved 10% or more IOP reduction from the baseline IOP at week 8 was 62.5%. The baseline IOP was significantly correlated with the percent IOP reduction at week 8 ($P = 0.03$, $r = 0.34$).

Conclusion: DTFC therapy added to PGAs as glaucoma monotherapy is effective in patients with normal tension glaucoma.

Keywords: IOP-lowering effect, prostaglandin, dorzolamide 1%/timolol 0.5% fixed combination, fixed combination, normal tension glaucoma

Introduction

Elevated intraocular pressure (IOP) is a known risk factor for glaucoma progression and reduction of IOP can prevent the progression of glaucomatous optic nerve damage and maintain the visual field.^{1,2} Normal tension glaucoma (NTG) is a disease characterized by progression of glaucomatous disorders despite the maintenance of IOP within the normal range. Nonetheless, reduction of the IOP is also important in the treatment of NTG, and it has been reported that the target reduction rate of IOP should be set at 30%.^{1,2}

Numerous reports have indicated that prostaglandin analog (PGA) therapies are effective in reducing IOP in NTG.³⁻¹² However, since PGAs produce only approximately a 20% reduction of IOP,³⁻¹² it is considered that the use of prostaglandin (PG) alone may be insufficient for obtaining the required 30% reduction of IOP, according to the reports of the Collaborative Normal-Tension Glaucoma Study Group.^{1,2} The majority of patients

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eventually require more than one medication to control their IOP. When IOP control is inadequate with PGAs alone, the addition of one of several therapies, including carbonic anhydrase inhibitor, timolol maleate 0.5%, and fixed combination therapies, has been shown to provide additional IOP control.^{13–17} However, it is yet unclear which of these therapies are superior in IOP control.

Treatment that is inconvenient or causes undesirable side effects encourages nonadherence in patients with glaucoma. By contrast, reducing the number of products and the number of required daily instillations increases patients' adherence.^{18–21} In recent years, various fixed combinations have been introduced in the market. Combining two medications in one bottle may reduce the time required to administer drops, the frequency or total number of drops, and the number of medication bottles. Therefore, the combination formulation may improve the rate of compliance and consequently improve IOP control.

There are many reports that have demonstrated the efficacy of these drugs in lowering the IOP in patients with primary open-angle glaucoma.^{13–17} However, there are no reports on the effect of the fixed combination of dorzolamide 1.0%/timolol maleate 0.5% (DTFC) (Cosopt[®]; MDS/Santen, Tokyo/Osaka, Japan) in NTG patients. In addition, there are also no reports on the additional IOP-lowering effect of DTFC in NTG patients treated with PGAs.

Therefore, in this study, the additive IOP-lowering effect of DTFC on PGAs monotherapy as the first-line therapy in Japanese patients with NTG was investigated.

Patients and methods

This was a prospective, clinical, case-controlled study undertaken from December 1, 2010 to May 30, 2011. The study followed the tenets of the Declaration of Helsinki and had the approval of the ethics committee of Mizoguchi Eye Clinic. Written informed consent was obtained from each patient before the start of the study.

Patients with NTG satisfying all of the following inclusion criteria were eligible for the study: (1) having had received PG as first-line glaucoma monotherapy; (2) in cases of bilateral NTG, the eye with higher IOP or the more advanced eye was selected; (3) aged 40 years or over; (4) refractive error of more than -6 dpt; (5) no history of previous treatment of glaucoma.

The exclusion criteria were: (1) patients with exfoliation syndrome; (2) patients with diabetic retinopathy; (3) refractive error of less than or equal to -6 dpt; (4) patients

with a history of ocular trauma, ocular inflammatory disease, glaucoma surgery, vitrectomy, and laser trabeculoplasty; (5) patients with conjunctivitis, dry eye or periocular cutaneous disease, possibly affecting the results of the investigation; (6) currently pregnant or nursing women, or women considering pregnancy were also excluded, as were patients with a history of noncompliance, or patients who had participated in another therapeutic drug study within 1 month; (7) history of cerebrovascular and hepatic disease.

NTG was diagnosed when glaucoma hemifield test results were outside the normal limits; the standard deviation had a P -value <0.05 ; or there was a cluster of three points or more in the pattern of the deviation plot, in a single hemifield, with a P -value <0.05 , one of which had to have a P -value <0.01 on the Humphrey Swedish Interactive Thresholding Algorithm 24-2 test (Humphrey Visual Field Analyzer, model 750, Humphrey Instruments, San Leandro, CA) and/or a nerve fiber layer defect combined with a corresponding optic disk change. In addition, the IOP measured by Goldmann applanation tonometer (Haag-Streit, Koniz, Switzerland) was consistently less than 21 mmHg. Gonioscopy excluded angle closure, rubeosis, and secondary glaucoma.

Patients who had previously received PG as glaucoma monotherapy, and needed to receive additive medications on PGAs monotherapy because of inadequate IOP reduction, were enrolled in the study. Twenty-four eyes were given tafluprost 0.005% (TAPROS[®]; Santen Pharmaceutical Co Ltd, Osaka, Japan), ten eyes were given latanoprost 0.005% (Xalatan[®]; Pfizer, Inc, New York, NY), and six eyes were given travoprost 0.004% (TRAVATANZ[®], Alcon Laboratories Inc, Fort Worth, TX). Patients received PG at a dose of one drop every evening (9 pm) to the study eye. IOP at the start of the study served as the baseline IOP. Once-daily administration (at 9 pm) of PG as monotherapy was continued and DTFC was added twice daily (9 am and 9 pm) for 8 weeks after the baseline visit. All patients enrolled in the study underwent a comprehensive ocular examination, including measurement of best-corrected visual acuity, slit lamp examination, and biomicroscopic fundus examination. Static gonioscopy was performed using Goldmann 2-mirror lens (Haag-Streit) at the first visit or before cataract surgery. IOPs were measured three times at 9 am using a Goldman applanation tonometer. If the difference in IOP between any two of the three measurements was greater than 3 mmHg, the median value was used. If it was less than 3 mmHg, the mean value was used.

Statistical analysis

Baseline and post-treatment values were compared by a one-way repeated-measures analysis of variance test. The difference in IOP was assessed by a paired *t*-test. Correlation between the baseline IOP and percent IOP reduction was analyzed by Spearman's correlation coefficient by rank test.

A *P*-value of <0.05 (two-tailed) was regarded as statistically significant. Statistical analysis was performed using Statistical Analysis System (v 8; SAS Institute Inc, Tokyo, Japan) software.

Results

In total, 44 patients (44 test eyes) were enrolled in this study. One patient dropped out of the study prematurely because of change of residence and discontinued their visit to the clinic. In three patients, treatment was discontinued because of the development of conjunctival hyperemia and ocular irritation. After excluding these four cases, 40 patients were included in the final analysis.

The demographic features are summarized in Table 1. All patients were Japanese. The mean age was 69.8 ± 12.0 years (range: 43–85 years). There were four males and 36 females.

Table 2 shows the IOP and the percent IOP reduction from the baseline IOP at weeks 4 and 8. Significant decrease of the IOP was observed at weeks 4 and 8 as compared with the baseline IOP (*P* = 0.01). The percent reduction from the baseline IOP at weeks 4 and 8 was 13.5% ± 12.3% and 11.7% ± 13.1%, respectively.

Table 3 shows the IOP and percent IOP reduction at each time point of measurement of the patient with a baseline IOP of 15 mmHg or higher (the high teens group) and those with a baseline IOP of less than 15 mmHg (the low teens group).

Table 1 Demographic characteristics of the participants in the study

Number of subjects	40
Male/female	4/36
Eyes	40
Age (y) (mean ± SD) (range)	69.8 ± 12.0 (43–85)
RE (D) (mean ± SD) (range)	−2.1 ± 3.5 (−6–+2.5)
MD (dB) (mean ± SD) (range)	−8.4 ± 0.37 (−24.5–0)
IOL (eyes)	10
Previous therapy	
Tafluprost	24
Latanoprost	10
Travoprost	6

Abbreviations: RE, refractive error; MD, mean deviation; IOL, number of patients after cataract surgery; SD, standard deviation.

Table 2 The mean intraocular pressure (IOP) and percent reduction (%) at each time point from baseline IOP

Time	Mean IOP (mmHg) (n = 40)
Baseline	15.6 ± 2.0
Week 4	13.5 ± 2.1*
Week 8	13.7 ± 2.2*
Percent reduction (%) in mean IOP from baseline	
Week 4	13.5 ± 12.3
Week 8	11.7 ± 13.1

Note: **P* = 0.01 vs baseline IOP, one-way repeated-measures analysis of variance.

In the high teens group, significant additional IOP reduction was observed at each time point of measurement as compared with the baseline IOP (*P* = 0.01). However, in the low teens group, there was no significant difference in the IOP from baseline IOP at any time point (*P* = 0.182). The percent reduction at week 8 from the baseline in the high teens group and the low teens group was 14.7% ± 11.7% and 6.6% ± 14.2%, respectively.

Tables 4 and 5 show the number and percentage of patients who achieved 10% or more, 20% or more, or 30% or more IOP reduction from baseline at week 8. The percentage of patients whose IOP reduction was 10% or more, 20% or more, or 30% or more was 62.5%, 22.5%, and 5%, respectively (Table 4). In the high teens group and low teens group, those were 72% and 53%, 32% and 13%, and 8% and 0%, respectively (Table 5).

Figure 1 shows the correlation between the baseline IOP and percent IOP reduction using Spearman's correlation coefficient by rank test. The baseline IOP was significantly correlated with the percent IOP reduction (*P* = 0.03, *r* = 0.34).

The most frequent adverse events related to the study medications were blurred vision, eye irritation, ocular

Table 3 The mean intraocular pressure (IOP) and percent reduction (%) at each time point from baseline IOP in the subgroups

Time	High teens group (n = 25)	Low teens group (n = 15)
	Mean IOP (mmHg)	Mean IOP (mmHg)
Baseline	16.8 ± 1.3	13.6 ± 0.9
Week 4	14.1 ± 2.1*	12.6 ± 1.8
Week 8	14.3 ± 2.1*	12.7 ± 2.1
Percent reduction (%) in mean IOP from baseline		
Week 4	16.3 ± 10.7	7.6 ± 13.4
Week 8	14.7 ± 11.7	6.6 ± 14.2

Notes: High teens group: baseline IOP was 15 mmHg or more, Low teens group: baseline IOP was less than 15 mmHg. **P* = 0.01 vs baseline IOP, one-way repeated-measure analysis of variance.

Table 4 The number of subjects who experienced a percentage decrease of intraocular pressure (IOP) at week 8 from baseline IOP

Percentage reduction after 8 weeks in mean IOP from baseline	No of subjects (%)
≥ 10%	25 (62.5)
≥ 20%	9 (22.5)
≥ 30%	2 (5)

hyperemia, and eye itching (Table 6). There were no systemic adverse events.

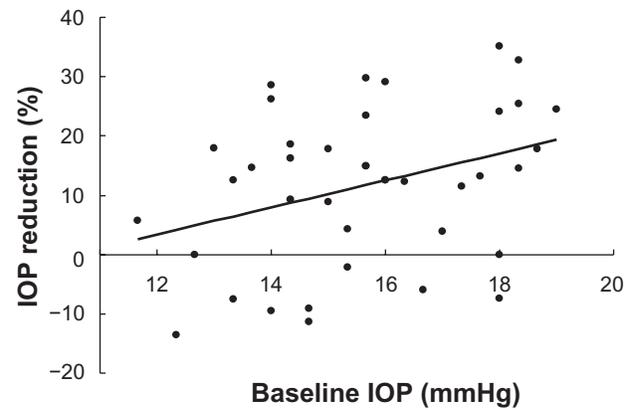
Discussion

A number of reports have indicated that DTFC might be effective in lowering the IOP in patients with glaucoma.^{13–17} In addition, there are reports that the IOP-lowering effect of the dorzolamide/timolol fixed combination may be equivalent to that of concomitant dorzolamide/timolol therapy, and other reports suggesting that the fixed combination therapy has a significant IOP-lowering effect.^{14,16,17} All these studies were conducted in patients with primary open-angle glaucoma who have elevated IOPs. There have been no reports on the efficacy of DTFC in NTG patients, reported for the first time in this study. The reported IOP-lowering effect of PG is approximately 20% in NTG patients, which suggests that PGA alone is insufficient for obtaining the target 30% or more reduction of IOP,^{3–11} according to the report of the Collaborative Normal-Tension Glaucoma Study Group.^{1,2} Glaucoma progression was seen significantly less frequently in the group in which a 30% or more IOP reduction was achieved, as compared with that in the group in which such reduction failed to be achieved.^{1,2} If the targeted IOP reduction can not be obtained with PGA monotherapy, additional medications are considered necessary. In this study, the IOP decreased significantly and remained low for 2 months with DTFC as second-line therapy, even in patients with NTG who had previously received IOP-lowering therapy with PGA. In 80%

Table 5 The number of subjects who experienced a percentage decrease of intraocular pressure (IOP) at week 8 from the baseline IOP in the subgroups

Percentage reduction after 8 weeks in mean IOP from baseline	High teens group (n = 25)	Low teens group (n = 15)
	No of subjects (%)	No of subjects (%)
≥ 10%	18 (72)	8 (53)
≥ 20%	8 (32)	2 (13)
≥ 30%	2 (8)	0 (0)

Notes: High teens group: baseline IOP was 15 mmHg or more, Low teens group: baseline IOP was less than 15 mmHg.

**Figure 1** The correlation between the baseline intraocular pressure (IOP) and percent IOP reduction by using Spearman's correlation coefficient by rank test.

Note: The baseline IOP was significantly correlated with the percent IOP reduction ($P = 0.03$, $r = 0.34$).

of the cases, DTFC have the capability to lower IOP even in patients with NTG. Thus, DTFC was found to have a favorable IOP-lowering effect. In addition, the drug combination produced an approximate additional 13% lowering of the IOP, as compared with the baseline IOP, suggesting that the administration of DTFC can be expected to produce an additional effect in patients in whom the target reduction rate (30%) of IOP has not been achieved by administration of PG alone. Konstas et al¹⁵ have reported that the administration of latanoprost and DTFC had the strongest IOP-lowering effect in patients with primary open-angle glaucoma, suggesting that administration of the DTFC in addition to PG might also produce a strong IOP-lowering effect in patients with NTG. However, it was also found that the administration of DTFC had no significant IOP-lowering effect in patients with IOP levels of <15 mmHg prior to the start of treatment, and no effect can be expected in such patients. The IOP was significantly reduced after additional instillation in NTG patients with baseline IOP of >15 mmHg prior to the additional instillation, therefore, additional instillation is considered to be effective in NTG patients with relatively high IOP levels. In addition, a significant correlation was found between the baseline IOP prior to the additional instillation and the percent IOP reduction from the baseline IOP; that is, the higher

Table 6 Adverse events

Event	Eyes (%)
Ocular hyperemia	1 (3%)
Eye irritation	3 (8%)
Eye itching	1 (3%)
Blurred vision	3 (8%)

IOP was prior to the start of the additional administration, the higher the percent IOP reduction from the baseline IOP. These results suggest that additional administration of DTFC is effective, and that it can improve the achievement rate of the target IOP in NTG patients, of which the targeted IOP could not be obtained with PGA monotherapy as first-line therapy.

It is considered important to determine the most effective PGs as the first-line medicine. If the target IOP cannot be achieved with PG monotherapy, additional instillation becomes necessary. It is reported that adherence to glaucoma medication is often poor.^{18–20} Multiple factors related to poor adherence have been identified, including more frequent¹⁸ and complex dosing.²⁰ Therefore, the number of medications should be reduced as much as possible for nonadherence patients. If IOP is inadequate with PGA as first-line medication, fixed combination should be added as second-line medication, because the therapy is less inconvenient.

With regard to safety, DTFC treatment is generally well tolerated. The most common adverse events in this study are eye irritation and blurred vision. All of the adverse events were mild. In this study, there was little change in the eyes after treatment compared with condition at the baseline period, suggesting that adverse events are unlikely to pose a significant clinical problem during use of DTFC.

Conclusion

This study suggests that a significant IOP-lowering effect can be obtained by instillation of DTFC in NTG patients in whom the target IOP has not been achieved by PG instillation alone. Furthermore, the higher the IOP prior to the additional administration, the higher the rate of reduction of IOP became. Taking treatment adherence into consideration, it was considered that DTFC was useful as a second choice drug for use in elderly patients with NTG after treatment with a PG preparation. However, the number of cases in this study was small, and further studies with a larger number of cases are considered necessary.

Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.

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