Hiroshima J. Med. Sci.
Vol. 59, No. 4, 71~75, December, 2010
HIJM 59–13

Efficacy and Safety of Topical Travoprost with Sofzia® Preservative for Japanese Glaucoma Patients

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ABSTRACT

The purpose of this study is to evaluate the intraocular pressure (IOP) –lowering effect and safety of topical travoprost with sofzia® and without benzalkonium chloride on Japanese patients with glaucoma. Topical travoprost (0.04%) was used on 39 glaucoma patients with no prior use of topical prostaglandin F2*a* analogues (Beginning group). The IOP, number of conjunctival follicules, degrees of conjunctival hyperemia, and degrees of superficial punctate keratitis (SPK, AD-classification) were determined at the beginning of the treatment and after 1 month and 3 months. 37 other patients who were using 0.005% topical latanoprost were switched to 0.04% topical travoprost and analyzed in the same way (Switched group). For the Beginning group, the IOP was significantly decreased after 3 months ($p < 0.0001$). The conjunctival follicule score was decreased significantly ($p = 0.033$). Both the SPK area score and density score for the cases with SPK at the baseline decreased significantly ($p = 0.034$ and $p = 0.024$). In the switched group, the IOP was not changed significantly at 3 months after the switch ($p = 0.118$). Both the conjunctival follicule and hyperemia score were significantly decreased at 3 month ($p = 0.0074$ and $p = 0.0047$). The SPK area score for the cases with SPK at the time of switch decreased significantly ($p = 0.013$). Travoprost with sofzia® preservative had an equal effect in reducing the IOP as latanoprost. It had low toxicity on the ocular surface of Japanese glaucoma patients.

Key words: *Travoprost, Glaucoma, Intraocular pressure, Safety, Sofzia®*

Topical application of prostaglandin F2*a* analogues increase the aqueous outflow from the eye through uveoscleral routes and are used to treat eyes with high intraocular pressures (IOP)[14]. Most glaucoma drugs, such as latanoprost and bimatoprost, are prostaglandin analogues and have excellent abilities to reduce the IOP. Thus, they are often the first choice in glaucoma therapy[13]. Travoprost is also a prostaglandin F2*a* analogue and reduces the IOP[1], and because of its biochemical properties, its effects are sustained for a long time[4]. It has been reported that topical travoprost has a greater effect in reducing the IOP than latanoprost in eyes with pseudoexfoliation glaucoma[7]. In addition, its effectiveness in reducing the IOP is comparable to that of the effects of travoprost in Asians with angle-closure glaucoma[3]. However, the evaluations of the effects of travoprost for reducing the IOP in Japanese patients have not been sufficiently investigated.

Most topical glaucoma drugs, such as latanoprost, use benzalkonium chloride (BAC) as a preservative. BAC has a direct antibacterial effect against bacteria and fungi but is toxic to normal conjunctivae and corneal epithelial cells[6]. On the other hand, sofzia® is a preservative composed mainly of zinc that has been used as a preservative in topical ophthalmic drugs. Zinc is ionized

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in a solution buffered with borate and sorbitol, and the ionized zinc inhibits the oxidative reaction of the NADH in bacteria and fungi. As a result, the activity of the bacteria and fungi declines and sofzia® acts as a preservative[12]. It has been reported that in rabbits, topical travoprost containing sofzia® has lower conjunctival toxicity than latanoprost containing BAC[5]. In addition, travoprost with sofzia® was found to be less likely to induce superficial keratitis[10]. It has been also reported that ophthalmic solution of travoprost containing sofzia® had lower cytotoxicity on human conjunctiva-derived cells than latanoprost [2]. Travoprost contains sofzia® instead of BAC as a preservative, but there are still many unknown aspects related to its effects on the human ocular surface.

The purpose of this study was to evaluate prospectively the IOP –lowering effect and safety on ocular surface agents of topical 0.04% travoprost preserved with sofzia® in Japanese glaucoma patients. To accomplish this, we studied one group of patients who had not used any type of prostaglandin F2α (Beginning group), and a second group who had been using topical 0.005% latanoprost and were switched to travoprost (Switched group).

METHODS

Patients

This was a nonrandomized, non-masked, multicenter, prospective, observational study. We studied 76 eyes of 76 glaucoma patients who were examined in our clinic between January and June 2008. There were 66 cases of primary open angle glaucoma, 4 with angle-closure glaucoma, 5 with pseudoexfoliation glaucoma, and 1 with developmental glaucoma. There were 30 male cases and 46 female whose range of age was from 23 to 85 years. The right eye was selected to be analyzed when both eyes received topical travoprost preserved with sofzia® (Table 1). All ophthalmic solutions that were being used before starting the travoprost were continued. There was no washout period when the treatment with topical latanoprost was switched to travoprost (Table 2).

The protocol of this study was approved by the Clinical Ethics Committee of Hiroshima University and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

Clinical examinations

The medical and ophthalmic histories were obtained at the baseline visit. A comprehensive ocular examination, including best-corrected visual acuity, slit-lamp examination for ocular- surface agents, IOP measurements by Goldmann applanation tonometry at 9:00 to 12:00 hr, and fundoscopy were performed at baseline visit and 1 month and 3 months after the beginning of the topical travoprost or after switching to travoprost from latanoprost. Automatic Humphrey visual field (program 24-2, Swedish interactive threshold algorithm standard) was also performed at the baseline visit and after 3 months.

The ocular -surface defects that were studied were: number of follicules on the palpebral conjunctiva (conjunctiva follicule), hyperemia of the bulbar conjunctiva (conjunctiva hyperemia), and superficial punctate keratitis (SPK). The conjunctiva follicules and hyperemia were evaluated with

Table 1. Demographic characteristics of study group

	Total		Beginning group		Switched group	
Charctersistics	(n)	Average ± SD	(n)	Average ± SD	(n)	Average ± SD
IOP (mmHg)	(76)	17.3 ± 3.51	(39)	18.1 ± 3.74	(37)	16.4 ± 3.10
Mean age (year)	(75)	65.0 ± 13.1	(38)	65.8 ± 12.9	(37)	64.2 ± 13.3
C/D ratio	(76)	0.76 ± 0.12	(39)	0.77 ± 0.113	(37)	0.76 ± 0.128
MD (dB)	(71)	-7.25 ± 7.78	(36)	-7.77 ± 6.27	(35)	-6.79 ± 8.96
PSD (dB)	(74)	7.75 ± 5.00	(37)	7.72 ± 4.95	(37)	7.78 ± 5.10

Values are the averages ± standard deviatio n of the mean (SD) with the numbers of subjects (n).
Beginning group is glaucoma patients with no history of use of topical prostaglandin F2α analogues, and Switched group is patients switching from topical latanoprost to topical travoprost.
IOP, intraocular pressure; C/D ratio, cup-to-disc ratio; MD, mean deviation for global index in the results of Humphery periphemetry; PSD, the pattern standard deviation.

Table 2. The concomitant use of topical medication for glaucoma

	Total	Beginning group	Switched group
None	42	24	18
Beta-blocker	18	14	4
Beta-blocker and carbonic anhydrase inhibitor	16	1	15

reference to standard photographs. The number of conjunctiva follicules were as: score 0 when none was present, score 1 when 1 to 9 follicules were present, score 2 when 10 to 19 follicules were present, and score 3 when > 20 follicules were present. The conjunctiva hyperemia was scored as: score 0 no hyperemia, score 1 when mild hyperemia was present, score 2 for moderate hyperemia, and score 3 for severe hyperemia. The degree of SPK was determined by comparing the appearance of the anterior segment to that of standard photographs. The AD classification, the area (score A) and density (score D), was used to evaluate SPK by fluorescein staining.

Statistical analysis

The IOPs and ocular surface agents in the Beginning group and Switched group were analyzed separately. The Friedman test was performed for the Beginning and Switched groups at the baseline and also 1 month and 3 months to determine the effect of travoprost on the IOP. Conjunctiva follicule score, conjunctiva hyperemia score, SPK area score, and SPK density score were statistically analyzed by Wilcoxon signed-ranks test at the baseline and 3 months. The effects of the concomitant use of eye-drops on the IOP were tested using repeated-measure ANOVA. The Stat View Software (Abacus Concepts Corp.) was used for all statistical analyses, and the significance level was set to a p value <0.05.

RESULTS

For beginning group, the average reduction of the IOP was 20.4% at 1 month and 21.0% at 3 months after the beginning of travoprost, and this was statistically significant. The decrease at both times was significant. The conjunctiva follicules significantly decreased in the score after 3 months. For the conjunctiva hyperemia, there was no significant change in the score after the travoprost. For SPK, both score A and score D had no significant change (Table 3). However, in the cases with SPK at the baseline, both score A and score D decreased significantly 3 months after travoprost (Table 4).

For the Switched group, the average reduction in the IOP was 4.3% at 1 month and 6.7% at 3 months after the switch. Both decreases were not significant. For conjunctiva follicules and hyperemia, both scores were significantly decreased after the switch to travoprost. For SPK, both score A and score D had no significant change (Table 5). But in the cases with SPK at the time of switch, the score A value decreased significantly after the

Table 3. Change of IOP and ocular-surface factors in the Beginning group

	(n)	Baseline	1 month	3 months	p value
IOP (mmHg)	(39)	18.1 ± 3.74	14.4 ± 3.48	14.3 ± 3.50	<0.0001
Scores of conjunctival follicule	(37)	0.33 ± 0.530	0.23 ± 0.427	0.13 ± 0.339	0.033
Scores of conjunctival hyperemia	(37)	0.33 ± 0.478	0.426 ± 0.720	0.333 ± 0.577	>.9999 (NS)
Score-A (SPK area score)	(38)	0.692 ± 0.614	0.436 ± 0.502	0.564 ± 0.552	0.244 (NS)
Score-D (SPK density score)	(38)	0.744 ± 0.715	0.436 ± 0.502	0.590 ± 0.595	0.218 (NS)

NS, not significant; IOP, intraocular pressure; SPK, superficial punctate keratitis.

Table 4. Details of change of ocular-surface factors in the Beginning group

		(n)	Baseline	1 month	3 months	p value
Scores of conjunctival follicule	Pre-conjunctival follicule (-)	(26)	0	0	0.07 ± 0.267	0.1573 (NS)
	Pre-conjunctival follicule (+)	(11)	1.08 ± 0.289	0.75 ± 0.452	0.25 ± 0.452	0.0039
Scores of conjunctival hyperemia	Pre-conjunctival hyperemia (-)	(26)	0	0.192 ± 0.491	0.192 ± 0.402	0.025
	Pre-conjunctival hyperemia (+)	(11)	1.00 ± 0.00	1.00 ± 0.816	0.615 ± 0.768	0.096 (NS)
Score-A (SPK area score)	Pre-SPK(-)	(15)	0	0	0.267 ± 0.458	0.046
	Pre-SPK(+)	(23)	1.13 ± 0.388	0.708 ± 0.464	0.750 ± 0.532	0.034
Score-D (SPK density score)	Pre-SPK(-)	(15)	0	0	0.267 ± 0.458	0.046
	Pre-SPK(+)	(23)	1.208 ± 0.509	0.708 ± 0.464	0.792 ± 0.588	0.024

Pre- means the measurement at the baseline, before the topical commencement of travoprost.

Table 5. Change of IOP and ocular-surface factors in the Switched group

	(n)	Baseline	1 month	3 months	p value
IOP (mmHg)	(37)	16.4 ± 3.10	15.7 ± 4.21	15.3 ± 2.80	0.1184 (NS)
Scores of conjunctival follicule	(36)	0.650 ± 0.770	0.225 ± 0.423	0.351 ± 0.484	0.0074
Scores of conjunctival hyperemia	(37)	0.700 ± 0.608	0.675 ± 0.764	0.432 ± 0.502	0.0047
Score-A (SPK area score)	(36)	0.500 ± 0.679	0.333 ± 0.577	0.378 ± 0.639	0.260 (NS)
Score-D (SPK density score)	(36)	0.550 ± 0.815	0.487 ± 0.914	0.595 ± 1.04	0.948 (NS)

Table 6. Details of change of ocular-surface factors in the Switched group

		(n)	Baseline	1 month	3 months	p value
Scores of conjunctival follicule	Pre-conjunctival follicule (-)	(18)	0	0	0.111 ± 0.323	0.157 (NS)
	Pre-conjunctival follicule (+)	(18)	1.300 ± 0.571	0.45 ± 0.510	0.579 ± 0.507	0.0011
Scores of conjunctival hyperemia	Pre-conjunctival hyperemia (-)	(12)	0	0.133 ± 0.352	0.167 ± 0.389	0.157 (NS)
	Pre-conjunctival hyperemia (+)	(25)	1.12 ± 0.332	1.00 ± 0.764	0.56 ± 0.507	0.0005
Score-A (SPK area score)	Pre-SPK(-)	(21)	0	0.042 ± 0.204	0.182 ± 0.502	0.103 (NS)
	Pre-SPK(+)	(15)	1.25 ± 0.447	0.800 ± 0.676	0.724 ± 0.724	0.013
Score-D (SPK density score)	Pre-SPK(-)	(21)	0	0.042 ± 0.204	0.227 ± 0.685	0.103 (NS)
	Pre-SPK(+)	(15)	1.38 ± 0.719	1.20 ± 1.15	1.13 ± 1.25	0.376 (NS)

Pre- means the measurement at the baseline, before the switch from latanoprost to travoprost.

switch (Table 6).

The concomitant use of eye-drops, beta-blocker or carbonic anhydrase inhibitor, did not affect the course of changes in IOP in either the Beginning group ($p = 0.117$) or Switched group ($p = 0.143$).

DISCUSSION

The IOP declined significantly after starting topical travoprost, and the amount of decrease was not significantly different from that with latanoprost. The conjunctival disorders that were present in eyes being treated with latanoprost were significantly ameliorated after switching to travoprost. In addition, the SPK observed before starting travoprost was decreased.

The average reduction in the IOP was 3.8 mmHg (21%) after starting travoprost. Studies conducted on non-Japanese showed that the average IOP was reduced by 6.1 mmHg (26%) after travoprost in open-angle glaucoma (OAG) patients with an average IOP at baseline of 23.6 mmHg[8]. The average IOP was reduced by 2.5 mmHg (17%) in cases of normal-tension glaucoma (NTG) with an IOP at the baseline of 15 mmHg[1]. For our patients, the IOP at the baseline was 18.1 mmHg, and the reduction in the IOP after was travoprost comparable to that in the earlier reports. At the same time, when switching from latanoprost to travoprost, the results were substantially similar to the results for non-Japanese patients. This indicates that for subjects including cases concomitantly using other eye-drops and in which the IOP at baseline was 16.4 mmHg, there were no significant differences in the IOP at 3 months after changing from latanoprost to travoprost[9]. Therefore, it is unlikely that the effects of topical travoprost in reducing the IOP in Japanese glaucoma patients were significantly different in patients outside of Japan. We believe that the effects of travoprost in reducing the IOP are similar to that of latanoprost 3 months after beginning the treatment.

Because follicules in the palpebral conjunctiva are sign of lymphocyte-based inflammation, they can be used as an indicator of the presence of inflammation. The hyperemia of the bulbar conjunctiva is also a sign of inflammation and cytotoxicity. Both the conjunctiva follicules and hyperemia scores at baseline were also improved after switching from latanoprost to travoprost. Thus, we can conclude that travoprost containing sofzia® has less irritation and toxicity effects on the conjunctival tissues compared to latanoprost containing BAC.

The AD classification is an established method for assessing corneal surface damage. The area and the density of fluorescein staining of the corneal surface are indicators to evaluate the severity of SPK[11]. After starting travoprost in the Beginning group, some cases developed SPK for the first time. However, their score was significantly lower than that of cases that had SPK before beginning of travoprost. Therefore, even though SPK may occur with travoprost containing sofzia®, the degree of SPK is suspected to be mild. Furthermore, in the Beginning group, the SPK area and density scores were significantly improved in those cases that had SPK before starting travoprost, as similar with previous report[15]. These results suggest that travoprost preserved sofzia® has a suppressing effect on SPK. Therefore, the toxic effect of topical travoprost preserved sofzia® on the corneal epithelial cells is reduced, and it can be considered to be particularly useful for cases with SPK.

In conclusion, topical travoprost preserved sofzia® had an equal effect in reducing the IOP with latanoprost and had low toxicity on the ocular surface. In the future, we believe that it is necessary to evaluate the long-term effects more than 3 months after commencement of both the first time use of travoprost and switching to travoprost from other anti-glaucoma medications.

(Received September 24, 2010)
(Accepted November 17, 2010)

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