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Short Tear Break-Up Time and Seasonal Variation in Intra-Ocular Pressure

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Abstract:

Purpose: To evaluate seasonal variation in intra-ocular pressure (IOP) with and without short tear break-up time (SBUT, BUT ≤ 5 s).

Methods: This study enrolled 176 patients who visited one of six eye clinics in Japan for IOP measurement at every season. The mean patient age was 67.9 years, including 79 males. We compared the seasonal variation in IOP (mean ± SD) across spring (Mar-May), summer (Jun-Aug), fall (Sep-Nov), and winter (Dec-Feb).

Results: The IOP (mmHg) in winter and summer, respectively, was 12.8 ± 3.7 and 12.8 ± 3.1 for non-glaucoma patients without SBUT (n = 47, P = 0.964), 14.8 ± 3.4 and 13.3 ± 3.4 for non-glaucoma patients with SBUT (n = 57, P < 0.001), 14.3 ± 3.2 and 14.1 ± 3.4 for glaucoma patients without SBUT (n = 36, P = 0.489), and 13.3 ± 3.0 and 11.6 ± 2.9 for glaucoma with SBUT (n = 36, P < 0.001). Seasonal variation was largest across the seasons in the glaucoma with SBUT group, and the magnitude of seasonal variation correlated with BUT (β = 0.228, P = 0.003).

Conclusions: Seasonal variation tended to be larger in patients with SBUT than those without SBUT.

Keywords: dry eye; tear break-up time; intra-ocular pressure; seasonality

1. Introduction

Glaucoma and dry eye disease (DED) are common geriatric diseases associated with poor quality of life and requiring ongoing daily topical medication [1,2] The prevalence of glaucoma and DED in middle aged and elderly Japanese is 4% and 12-23%, respectively,[3,4] making both disorders a common presentation in daily

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ophthalmic practice. In addition, glaucoma and DED frequently co-exist in a single patient, and some of the glaucoma medications can affect the ocular surface as a side effect [5]. For this reason, glaucoma medication comes in a preservative-free, single dose unit, with reduced toxicity from chlorhexidine and SofziaR, and a decreased concentration of benzalkonium chloride (BAK), the most commonly used preservative in such agents. DED is also a multifactorial disease that predominantly affects women and the elderly, rheumatoid disease, and immunological disease, and that generally worsens in both prevalence and severity during cold and dry weather.[6-10] DED patients can have wide variety of symptoms and ocular surface signs, but short tear break-up time (BUT) has been introduced as a representative sign in most recent diagnostic criteria.[2]

There are many risk factors for glaucoma in terms of ocular hypertension and optic nerve damage,[11-14] with seasonality in intra-ocular pressure (IOP) well documented as well as higher IOP with hypertension and cold weather.[15-21] Clinically, it is unknown whether DED may alter IOP and therefore glaucoma, since both conditions worsen in winter, and both IOP and lacrimal secretion are under neural control.[22] Consequently, IOP control should be given special attention across all seasons. To investigate the clinical importance of IOP with and without DED, we compared seasonality between short and normal BUT cases with and without glaucoma. The obtained results should provide useful information for IOP control in these common diseases.

2. Methods

2.1.Study Design, Ethical Approval, and Study Population

This study was a multisite, hospital-based, cross-sectional, case-control study conducted from March 2015 to February 2017. The cases and control subjects were recruited from six clinical sites: Komoro Kosei General Hospital (Nagano, Japan), Shinseikai Toyama Hospital (Toyama, Japan), Tsukuba Central Hospital (Ibaraki, Japan), Jiyugaoka Ekimae Eye Clinic (Tokyo, Japan), Todoroki Eye Clinic (Tokyo, Japan), and Takahashi-Hisashi Eye Clinic (Akita, Japan).

This study was done on mainland Japan, where the latitude is 35.68 degrees North in the Tokyo area and day length varies by 4–6 hours over the year according to averages for 1981–2010 reported by the Japan Meteorological Agency. Japan has four distinct seasons during which the temperature, humidity, and daylight time markedly varies. Between 1981 and 2010, the average temperature and humidity in the Tokyo area ranged from 5.2°C and 52% in winter to 25.0°C and 77% in summer, in Akita from 0.1°C and 73% in winter to 22.9°C and 79% in summer, in Toyama from 2.7°C and 79% in winter to 24.6°C and 78% in summer, and in Komoro from -0.6°C and 78% in winter to 23.8°C and 74% in summer, respectively, as reported by the Japan Meteorological Agency.

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The respective institutional review boards and ethics committees of Shinseikai Toyama Hospital (Permit Number: 150503) and Komoro Kosei General Hospital (Permit Number: 2705) approved this study, which was conducted in accordance with the tenets of the 1995 Declaration of Helsinki (as revised in Edinburgh, 2000). Informed consent was obtained from all participants.

Participants were divided into four groups based on the presence of glaucoma and/or short BUT (≤ 5 seconds); non-glaucoma with normal BUT as control group, non-glaucoma with short BUT group, glaucoma without short BUT group, and glaucoma with short BUT group.

2.2.Inclusion and exclusion criteria

Patients were enrolled if they had their IOP measured during four consecutive seasons and received the same medication during the study period. Study participants visited our clinic for regular checkups for early cataract, eye fatigue, DED, and glaucoma. Patients were excluded from the study if they had visual impairment (< 20/25 in either eye) or were under 20 years of age. Patients were excluded from the study if they had history of past glaucoma surgery, or any ocular surgery within twelve months. We excluded patients from glaucoma cases if they have secondary glaucoma, uveitis, or steroid administration.

2.3.Ophthalmological examinations

IOP was measured in the morning session between 8 am and 12 midday, using a non-contact tonometer in all cases. The mean BUT and corneal staining scores (0-9 points) were based on the Japanese dry eye diagnostic criteria,[23] with BUT evaluated three times, and the mean value determined. Corneal fluorescein staining scores were evaluated in three areas and scored on a 0- to 2-point scale (0: no damage to 2: damaged entirely); the scores were summed up to a maximum of 2 points in total. Ocular surface abnormality was defined as a BUT ≤ 5 seconds and corneal staining scores ≥ 1 point based on previous studies.[24,25]. The BUT and corneal fluorescein staining score were determined at the date of each patient's visit in year 2017 and classified as follows: spring from March to May, summer from June to August, fall from September to November, and winter from December to February.

All glaucoma cases were bilateral open angle glaucoma or normal tension glaucoma. For glaucoma diagnosis, we conducted a visual field test (Humphrey Visual Field Analyzer 30-2 standard program; Carl Zeiss, Jena, Germany), measuring the thickness of ganglion cell complexes using optical coherent tomography (OCT;

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RC3000R (Nidek, Gamagori, Japan) and Cirrus® HD-OCT (Carl Zeiss, Jena, Germany)), and then routine examinations were performed. As described previously [24], diagnostic criteria for glaucoma in the present study comprised glaucomatous visual field loss tested using the Glaucoma Hemifield Test, an ophthalmoscopic neurofiber layer defect, a cup/disc ratio > 0.6, or elevated IOP (> 21 mmHg) requiring topical medication for more than 6 months. We confirmed no change in glaucoma medication during study period with chart review. Exclusion criteria were coexisting cataract with significant lens opacity disturbing the optical axis that accounted for subjective visual disturbance or decreased visual function, retinal pathology, retinal surgery, or photocoagulation affecting the visual field. Topical glaucoma medications were listed in Table S1.

3. Statistical analysis

The effects of each season on the IOP were compared as follows. Based on a preliminary study and previous investigations suggesting that IOP is highest in winter and lowest in summer, we identified the mean IOP for each season and then compared summer and winter using by t-test or Mann-Whitney U test with Bonferroni correction to determine if the differences between seasons were significant. Mean IOP and the magnitude of seasonality among the four study groups were also compared. Regression analysis was performed to explore which parameters most affect the magnitude of seasonal difference in IOP. Ophthalmological parameters and glaucoma medications were analyzed with multiple regression from the first analysis since most cases were prescribed with PG as a baseline and beta blocker and CAI were often concomitantly prescribed. Data are presented as the mean ± standard deviation (SD) or as percentages where appropriate. All analyses were performed using StatFlex (Atech, Osaka, Japan), with $P < 0.05$ considered significant.

4. Results

The characteristics, ophthalmological results and DED-related medications of 176 patients enrolled in this study (79 males and a mean age of 67.9 years) are detailed in Table 1. The corneal staining score was higher in groups with short BUT compared with the control group. Non-glaucoma with short BUT group was prescribed more dry eye medications compared with the other groups; more than half (56%) of them received DED-related medications and 17-31% of patients in the other groups. Steroid eye-drops were used only for non-glaucoma groups. The distribution of seasons for BUT determination was similar in short and normal BUT groups (P=0.305 for non-glaucoma groups and P=0.118 for glaucoma groups, Mann-Whitney test) and there was a difference between glaucoma and non-glaucoma group (P=0.010, Kruskal Wallis test).

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Prostaglandin analogues provided a first-line medication for 97.2% (70/72) of glaucoma patients and beta-blockers were prescribed for 25 cases (34.7%; Table S1). The mean number of eye-drops was 1.4 ± 0.7 for glaucoma without short BUT group and 1.2 ± 0.5 for glaucoma with short BUT group (P = 0.342, Kruskal Wallis test), and the mean frequency of instillation was 1.4 ± 1.0 for glaucoma without short BUT group and 1.7 ± 1.3 for glaucoma with short BUT group (P = 0.416). Monotherapy was administered for 28 cases (77.8%) of glaucoma without short BUT group and 27 cases (75.0%) of glaucoma with short BUT group. All of prescribed glaucoma medications contained benzalkonium chloride or other preservative; SofZiaR in TravatanzR and PolyquadR in DuotravR.

Mean IOP was significantly different between winter and summer in the short BUT groups (P < 0.001 for both glaucoma and non-glaucoma groups, paired t test), but not for the normal BUT groups (P = 0.964 for control group and P = 0.489 for glaucoma group)(Table 2). The mean magnitude of seasonality (winter-summer) was greater in short BUT groups than control, and it was largest in the glaucoma with short BUT. Comparison of IOP across seasons between glaucoma groups revealed significantly lower IOP in the short BUT group for all seasons except winter.

The individual range of IOP was smaller for the glaucoma groups than the non-glaucoma groups as indicated in minimum and maximum inter-individual variation across four seasons; 10 and 10 mmHg for glaucoma groups with and without short BUT, respectively, and 17 and 20 mmHg for non-glaucoma groups. The graphic representation of the magnitude of seasonality are shown in Figures 1 and S1.

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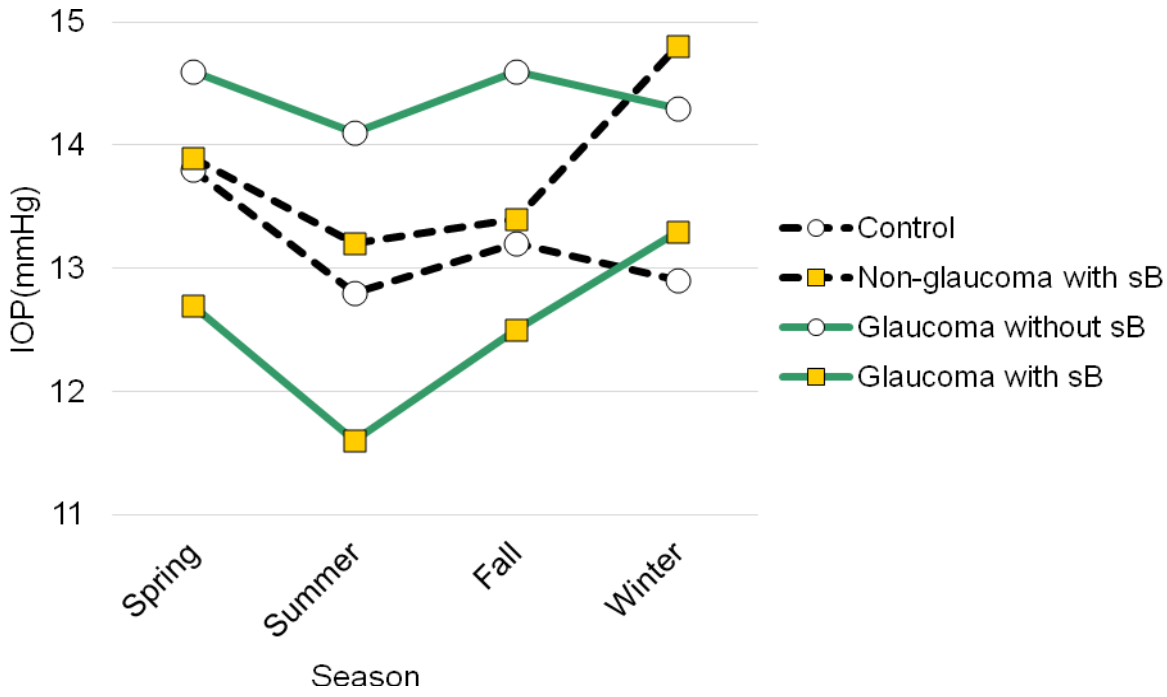

Figure 1. Seasonal variation in intra-ocular pressure (IOP).

Mean IOP value in each group presenting for IOP measurements was higher in winter than in summer. Study groups with short tear break-up time (sB) showed larger fluctuation than those groups without sB.

Table 1. Demographics and dry eye medication in each group.

	Control	Non-glaucoma with sB	Glaucoma without sB	Glaucoma with sB
# Participants	47	57	36	36
Age (years)	71.5 ± 14.1	66.5 ± 15.3 (0.144)	64.1 ± 13.8 (0.028)	71.1 ± 13.6 (1.000)
% of men	44.7	24.6 (0.030)	75.0 (0.010)	47.2 (0.818)
Refractive errors (diopter)	-0.68 ± 2.78	-1.41 ± 2.85 (1.000)	-2.77 ± 3.64 (0.022)	-1.96 ± 3.40 (0.191)
# eyes with IOL (0/1/2)	37/6/4	44/3/10	30/2/4	24/4/8
Corneal staining score	0.09 ± 0.35	0.37 ± 0.61 (0.018)	0.17 ± 0.38 (0.913)	0.53 ± 0.74 (0.002)
Dry eye medication (%)				
None	76.6	43.9 (0.001)	83.3 (0.451)	69.4 (0.464)
Hyaluronate	10.6	21.1	11.1	19.4
Mucin secretagogue	14.9	35.1	5.6	11.1
Steroid	4.3	10.5	0	0
Season of visit to determine BUT				

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Spring	0	1	3	5
Summer	44	48	16	22
Fall	2	1	6	4
Winter	1	7	11	7
Glaucoma parameters				
Mean deviation (dB)			-4.46 ± 5.76	-5.61 ± 5.14 (0.386)
Disc cupping (%)			73.2 ± 16.8	75.7 ± 17.8 (0.957)

P value compared with control in parentheses, using the tests for significance were Mann-Whitney U test with Bonferroni correction for continuous variables and Chi-square tests for categorical variables. Abbreviations; sB, short tear break-up time; BUT, tear break-up time; IOL, intra-ocular lens.

Table 2. Mean intra-ocular pressure (mmHg) in each season.

	Control	Non-glaucoma with sB	Glaucoma without sB	Glaucoma with sB	*P* value[C]	*P* value[D]
Spring	13.8 ± 3.3	13.9 ± 3.5	14.6 ± 3.3	12.7 ± 3.0	0.973	0.021
Summer	12.8 ± 3.1	13.3 ± 3.4	14.1 ± 3.4	11.6 ± 2.9	0.747	0.001
Fall	13.2 ± 3.1	13.4 ± 3.4	14.6 ± 3.9	12.5 ± 3.1	0.844	0.008
Winter	12.8 ± 3.7	14.8 ± 3.4	14.3 ± 3.2	13.3 ± 3.0	0.218	0.112
P value (summer vs winter)	0.964	<0.001	0.489	<0.001		
Mean magnitude of seasonality[A] (mmHg)	0.0 ± 3.2	1.5 ± 2.8 (0.023)	0.2 ± 2.1 (1.000)	1.7 ± 2.3 (0.032)	0.091	0.009
Highest seasonality[B]	8	7	5	6		
Lowest seasonality	-12	-10	-5	-4		
Range (highest-lowest)	20	17	10	10		

[A]*P* value compared with control in parentheses, using Mann-Whitney U test with Bonferroni correction. [A]=(winter-summer), [B]=maximum value of the magnitude, [C]=control vs non-glaucoma with sB, [D]=glaucoma without sB vs glaucoma with sB. Abbreviations: sB, short tear break-up time.

Linear regression analysis revealed that the magnitude of seasonality in IOP was correlated with BUT and the number and frequency of medication, whereas it was not correlated with age, sex, corneal staining score, mean deviation, refractive errors, and the type of medication (Table 3). Multiple regression analysis demonstrated BUT was most strongly correlated with seasonality among three variables.

Table 3. Regression analysis of the magnitude of IOP and parameters.

	Linear regression		Adjusted for age and sex	
	β	*P*-value	β	*P*-value
Age	-0.077	0.519		
Sex[A]	0.019	0.874		
Model 1: Corneal parameters				
Tear break-up time (sec)	-0.224	0.003*	-0.237	0.002*
Corneal staining score	0.100	0.403	0.126	0.107
Model 2: Glaucoma-related parameters				

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Beta blocker	0.084	0.581	0.067	0.662
Carbonic anhydrase inhibitor	0.128	0.399	0.156	0.320
Number of medications	0.269	0.022*	0.266	0.025*
Frequency of medication	0.246	0.037*	0.247	0.039*
Refractive error (D)	0.007	0.929	-0.044	0.569
Mean Deviation (dB)	-0.123	0.320	-0.136	0.281
Disc cupping (%)	-0.063	0.617	-0.049	0.712
Multiple regression	Non-adjusted		Adjusted for age and sex	
Tear break-up time	-0.292	0.011*	-0.356	0.004*
Number of medications	0.372	0.346	0.237	0.572
Frequency of medication	-0.141	0.720	-0.013	0.973

[A]male = 1; female = 0. *$P < 0.05$.

Abbreviations: CAI, carbonic anhydrase inhibitor; NFL, thickness of peripapillary nerve fiber layer.

4. Discussion

The present results indicated the following two major findings: seasonality of IOP was greater with a short BUT compared to normal BUT, and IOP was lower with short BUT than with normal BUT. Based on the reported seasonal variation in DED,[7] the Schirmer test value was worst in winter, with BUT and corneal staining scores the second worst in winter for DED patients. In contrast, all of the corneal signs were less severe in summer. It is notable that seasonal variation in IOP in our study was similar to that reported for corneal staining score in a DED group described previously.[7] Corneal damage induce inflammation on the ocular surface leading to IOP increases mediated by bioactive molecules including TGF beta [26,27] and prostaglandins.[28] Distress associated with uncomfortable symptoms including irritation, pain, and dryness could also raise IOP, particularly because depression is prevalent in DED patients and worsens in winter, and thus this state might result in ocular hypertension. [29-32] Such an outcome might also explain the IOP reduction noted in summer when the corneal staining scores and DED symptoms are least severe. IOP and blood pressure are positively correlated and increased in winter,[13,14] and adrenergic receptor activation has been conventionally proposed as a possible regulatory system for this phenomenon.[33] IOP fluctuations are generally differentiated in short-term (diurnal) and long-term IOP fluctuations (months – years) and the seasonal

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IOP fluctuation is the latter one. Our results suggested it could be present in both glaucoma and non-glaucoma cases.

The present results indicated that IOP was lower in cases with short BUT than in those with normal BUT, and this difference was larger between glaucoma groups than between non-glaucoma groups. Taken together, lower IOP values and larger winter IOP rises were predominantly observed in glaucoma cases with short BUT. This is paradoxical since if IOP increases with worsening of DED in the cold and dry weather of winter, IOP in short BUT should be higher than in normal BUT for all seasons. A possible explanation for this seeming anomaly is cornel thinning and drug penetration facilitated by disruption of the ocular surface barrier effects in DED as previous investigations suggested IOP may be estimated for lower value in thin cornea and intra-ocular drug effects of instilled eyedrop depend on drug penetration.[12,34,35] Sleep disorder, depression, and possible decreases in melatonin secretion could also contribute to the dysregulation of IOP[36] in winter when sunshine decreases and DED patients may suffer more stress and worsened symptoms.

Our study has several limitations. First, because this is an observational study, unmeasured or residual confounding factors may remain. Nonetheless, our multivariable adjusted analyses of major possible contributory factors should attenuate potential errors. Second, there is a fundamental limitation in the lack of data for corneal thickness and blood pressure because we failed to confirm whether thinner corneal thickness in DED including cases with short BUT and seasonal variation in blood pressure were directly attributed to the seasonal variation in IOP or other relevant neuronal factors such as use of neuronal or psychiatric medications in glaucoma cases. Therefore, future longitudinal studies with systemic evaluations of neuronal aspects are necessary to gain an understanding of seasonal IOP variation in glaucoma patients with short BUT. Third, because the majority of our participants were Japanese, our data may lack generalizability. Hence, additional studies performed in patients with different ethnicities are warranted to investigate the association between seasonality and BUT. Thus, we interpreted age-/sex- adjusted and multivariable-adjusted models in addition to univariable model results with some caution. Fourth, we should have used Goldmann tonometer as a gold standard for IOP measurement, however, we believe IOP data was obtained accurately enough for our study since most examinations were performed by certified orthoptists (national licensure) and we analyzed the mean IOP of three measurements. Finally, potential selection bias and heterogeneity among intergroups might not be completely eliminated, although the distribution of baseline characteristics for age and sex were reasonable in that more women were included in the short BUT groups and more myopic subjects were included in the glaucoma groups. Also, our study examined BUT once at the time of study entry and BUT values can vary among seasons on an individual basis. Thus, BUT and IOP could be measured in each season and a mixed effect

model applied, although the distribution of the season for BUT measurement was uniformly distributed in the present study enabling us to address this issue.

This study has several strengths. First, this study was conducted in Japan with four distinct seasons presenting various temperature and humidity fluctuations. Second, the samples were collected from multiple institutions in Japan, allowing us to conduct a case-control study including enriched ophthalmic parameters in a rigorous manner. The novelty of our current study is that we successfully capture the distinctly enhanced seasonal variation in glaucoma patients accompanied with short BUT-type DED, with being very common and severely affecting quality of life through eye disease. Additionally, the present results were demonstrated as comparable with those of a large-scale study over 4000 cases to minimize a variety of bias.[37] In a large-scale study we examined each patient once to immediately correlate IOP with DED, and the present study was carried out in a standard method with repeated examinations on the same patients to adequately analyze seasonal variation.

In conclusion, the eye care specialists should be careful of IOP in glaucoma cases with short BUT since seasonal IOP fluctuation may be greater than normal BUT cases and special attention should be paid for IOP rise in winter. BUT measurement could be recommended in glaucoma cases since any glaucoma medication may cause or aggravate DED and it could be associated with considerable IOP fluctuation.

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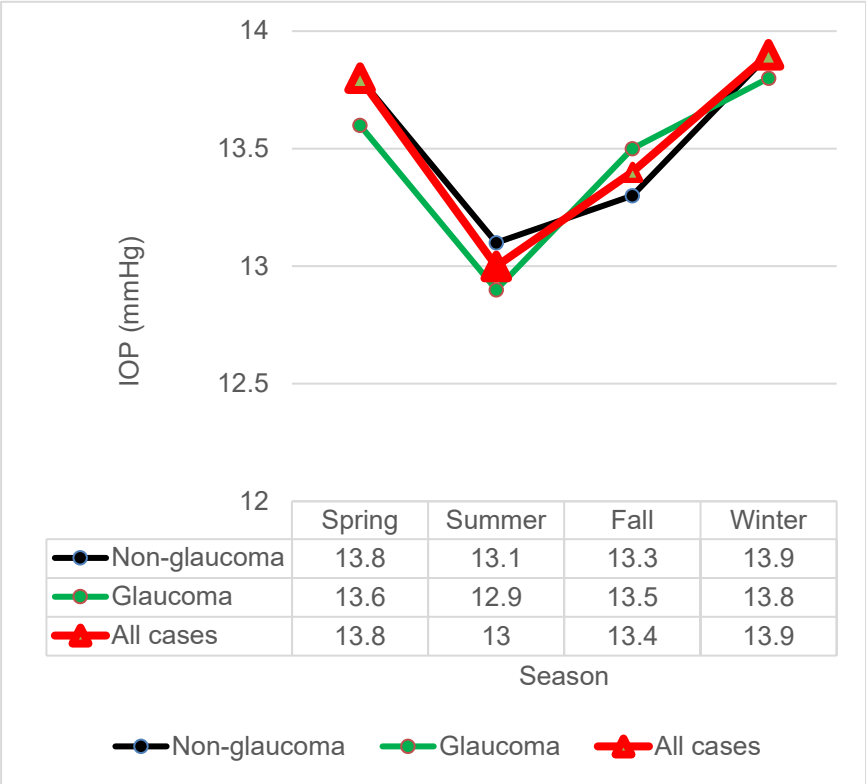

Figure S1. Intra-ocular pressure (IOP) of glaucoma and non-glaucoma groups

Table S1. Glaucoma medications in each group.

		Glaucoma without short BUT	Glaucoma with short BUT
# of medication	1	28	27
	2	7	5
	3	1	4

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		Mean*	1.4 ± 0.7	1.2 ± 0.5
Frequency of instillation		1	27	27
		2	4	1
		3	3	4
		4	1	1
		5	1	3
		Mean**	1.4 ± 1.0	1.7 ± 1.3
Medications	PG	Latanoprost	21	20
		Tafluprost	8	11
		Travoprost	3	3
		Bimatoprost	2	2
	Fixed combination	PG/timolol	2	6
		CAI/timolol	5	6
	Beta blocker	Timolol	10	15
		Carteolol	0	1
	CAI	Dorzolamide	5	5
		Brinzomide	0	3
	Other[A]		0	4

[A] = Brimonidine tartrate for three and ripasudil hydrochloride hydrate for one. Abbreviations; BUT, tear break-up time; PG, prostaglandin analogue; CAI, carbonic anhydrase inhibitor. *P = 0.342, **P = 0.416 (Kruskal-Wallis).

All of prescribed glaucoma medications contained benzalkonium chloride or other preservative; SofZia in travoprost eyedrop and Polyquad in fixed combination with travoprost and timolol maleate. Active compounds of glaucoma medication prescribed in the present study are as follows: 0.005% latanoprost, 0.0015% tafluprost, 0.004% travoprost, 0.003% bimatoprost, fixed combination of 0.005% latanoprost and 0.5% timolol maleate, fixed combination of 0.0015% tafluprost and 0.5% timolol maleate, fixed combination with 0.004% travoprost and 0.5% timolol maleate, fixed

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combination with 0.5% timolol maleate and 1% dorzolamide hydrochloride, 1% brinzolamide, 1% dorzoramide hydrochloride, 0.1% brimonidine tartrate, 2% carteolol hydrochloride, 0.4% ripasudil hydrochloride hydrate, and 0.5% timolol maleate.