의학석사 학위논문

Effect of Long-term Intraocular Pressure Fluctuation on the Rate of Glaucomatous Progression in Myopic Normal-Tension Glaucoma

근시 정상안압녹내장에서 장기 안압변동이 녹내장 진행 속도에 미치는 영향

2019 년 12 월

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December 2019

Department of Ophthalmology,

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by
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Approved by Thesis Committee:

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ABSTRACT

Purpose: To investigate whether the association of long-term intraocular pressure (IOP) fluctuation with the rate of progression of normal-tension glaucoma (NTG) is modified by myopia.

Design: Observational case series study.

Methods: The medical records of 65 myopic NTG (axial length >24.0 mm) and 64 non-myopic NTG eyes (axial length <24.0 mm), who had been treated with topical medications for more than 5 years, were reviewed. Multiple linear regression models were fitted to analyze the relationships of the slope of mean deviation (MD) or visual field index (VFI) with the clinical factors, including the interactions with myopia.

Results: The average follow-up period was 8.3 years. Twenty-two (22) non-myopic eyes (34.4%) and 27 myopic eyes (41.5%) showed NTG progression (P = 0.511). The interaction of myopia with IOP fluctuation was a significant factor regarding both MD and VFI slope (P = 0.002, 0.024, respectively); stratified analyses suggested that the risk effect of IOP fluctuation was significant only in myopic NTG in terms of both MD (β = -1.27, P = 0.003) and VFI slope (β = -2.32, P = 0.011).

Conclusions: IOP fluctuation was significantly related to the rate of VF progression in myopic NTG compared with non-myopic NTG.

Keywords:

Intraocular pressure Fluctuation Myopia Normal-Tension Glaucoma Progression

CONTENTS

INTRODUCTION

Glaucoma is a chronic optic neuropathy that is characterized by progressive axonal loss and retinal ganglion cell damage.[1] The sole evidence-based treatment for glaucoma is intraocular pressure (IOP)-reducing therapy. As there is much well-established evidence of a link between increased IOP and visual field (VF) deterioration, lowering of IOP can slow such progression even in cases of normal-tension glaucoma (NTG).[2-4]

While there are many previous reports supporting the association between lowered mean IOP with medical or surgical treatment and protection against glaucoma progression, the significance of short-term or long-term IOP fluctuation remains controversial, due to the differences among study populations, disease entities (high-tension glaucoma [HTG], NTG, or primary angle-closure glaucoma [PACG]), and indeed the definitions of fluctuation of IOP itself.[5, 6]

Myopia is a well-known risk factor for glaucoma development.[7-10] However, its role in glaucoma progression is controversial. Many studies have proposed that myopia and high myopia are risk factors for glaucoma progression.[11-14] However, other studies have reported that myopia does not affect glaucoma progression and that in fact, it might act as a protective factor for NTG progression.[15-17]

There have been several attempts to identify clinical factors associated with glaucoma progression rates. [11, 18, 19] However, most of the previous studies compared the progression rate according to mean IOP (i.e. HTG vs. NTG), or a type of glaucoma (i.e. primary open-angle glaucoma [POAG] vs. PACG). Myopia is associated with anatomic weakness of the optic nerve head[20] or altered circulation including reduced blood flow[21] and low ocular pulse amplitude.[22] In this aspect, the impact of IOP-related factors on the optic disc in myopic eyes might differ from the case of non-myopic eyes. Thus, understanding the clinical factors associated with progression rate according to the presence of myopia may be significant to clinical practice.

In the present study, we examined both the VF progression rate of NTG according to the presence of myopia and how myopia modified the IOP-related factors' associations with functional deterioration.

MATERIALS AND METHODS

The present research followed the tenets of the Declaration of Helsinki, the study protocol having been approved by the local ethical committee of Seoul National University Hospital. Informed consent was waived due to the retrospective nature of the study.

Subjects

The subjects in the study were chosen from Seoul National University Hospital (Korea)'s Glaucoma Clinic database representative of the years 2005 to 2013. Patients who had had their NTG treated with medication and been followed up on for more than 5 years were enrolled. In cases where glaucoma surgery had been performed, the follow-up period was ended. All of the subjects had undergone common ophthalmologic examinations, including best-corrected visual acuity measurement, intraocular pressure (IOP) measurement by Goldmann applanation tonometry, refractive error measurement with an autorefractor (KR-890; Topcon Corporation, Tokyo, Japan), corneal pachymetry (Pocket II Pachymeter Echo Graph; Quantel Medical, Clermont-Ferrand, France), slit-lamp biomicroscopy, gonioscopy, and dilated fundus examination. The subjects also underwent stereo optic disc photography, red-free RNFL photography (Vx-10a; Kowa Optimed Inc., Tokyo, Japan or Visucam 524; Carl Zeiss Meditec, Dublic, CA, USA), axial length (AL) measurement (Axis II PR; Quantel Medical, Inc., Bozeman, MT, USA), as well as SAP using the Swedish interactive threshold algorithm according to the central 30-2 or 24-2 standard program (Humphrey Field Analyzer II; Carl Zeiss Meditec, Dublin, CA, USA). The occurrence of disc hemorrhage (DH) was also evaluated at every visit using direct ophthalmoscopy or stereo optic disc photography.

The inclusion criteria were as follows: 1) age between 30 and 85 at initial examination, 2) best corrected visual acuity of ≥20/40, 3) maximal IOP without treatment ≤21 mmHg, 4) no history or evidence of retinal diseases or non-glaucomatous optic nerve diseases, 5) open angle by gonioscopy, 6) follow-up period ≥ 5 years and at least 5 reliable VF results. The exclusion criteria were as follows: 1) high myopia (AL ≥ 28.00 mm), 2) baseline MD <-15.0 dB, 3) severe media opacity, or 4) any history of ocular surgery except uncomplicated cataract surgery. In cases where both eyes of a subject were eligible for the study, one eye was randomly chosen for inclusion.

Visual Field (VF) Examination

VF status was assessed by SAP twice at an interval of 3 months for the baseline, and then every 6 to 12 months for at least 5 years. VF assessment was performed with optical correction [23]. The refractive correction was calculated with the internal algorithm of the Humphrey Field

Analyzer, and full refractive correction was performed with trial lenses. Glaucomatous VF defects were defined as (1) outside normal limits on glaucoma hemifield test; (2) 3 or more abnormal points with <5% probability of being normal, of which at least 1 point has pattern deviation of P < 1%; or (3) pattern standard deviation (PSD) < 5%. VF defects had to be repeatable on at least 2 consecutive tests. Only reliable VF results were included for subsequent analysis (fixation loss rate <20%, false-positive and false-negative error rates <25%).

Diagnosis of myopic and non-myopic NTG

Diagnosis of NTG was based on the presence of glaucomatous VF loss on SAP as described above, on the presence of glaucomatous optic disc cupping (i.e. neuroretinal rim thinning, notching, excavation) or RNFL defect, and maximum IOP ≤21 mmHg. Patients were divided into 2 diagnostic groups, according to the axial length and refractive error: the myopic NTG group, with AL >24.00 mm, and the non-myopic NTG group, with AL <24.00 mm.

Determination of rate of progression of NTG

The rate of progression was defined by the slope magnitude of mean deviation (MD) and visual field index (VFI), as calculated by linear regression analysis with the trend-based Guided Progression Analysis (GPA) software from the Humphrey Field Analyzer. VFI is the aggregate percentage of the remaining VF in the pertinent eye.[24] The first 2 to 4 VF results were excluded in order to minimize learning effects. Any unreliable results, as defined above, also were excluded.

Since trend-based GPA provides only the slope magnitude, with no simple judgment of progression, NTG progression was additionally categorized as “likely progression” on event-based GPA, defined as a significant decrease from the baseline (two examinations) pattern deviation at three or more of the same test points on 3 consecutive VF tests according to the early manifest glaucoma trial (EMGT) criteria.[25]

Statistical analysis

We used the independent t-test and chi-square test to compare the clinical characteristics of the two groups. Fluctuation of IOP was defined as its standard deviation during treatment. Percentage of IOP reduction was defined as 100×(IOP without treatment–mean IOP during treatment)/baseline IOP.[2] Peak and trough IOPs were defined by maximum and minimum IOPs during treatment, respectively. Because more than one month of treatment may be needed to attain the full IOP-lowering effect with medication,[26, 27] IOP readings during treatment were collected at least 2 months after starting medication.

Multiple linear regression models were fitted to assess the associations of the clinical factors with the slope magnitude of MD and VFI, including the interactions of IOP-related factors with myopia, so as to confirm that myopia modified the associations between the IOP-related factors

and the rate of progression. A subsequent stratified analysis according to myopia was performed for both groups to calculate the coefficients (β) with 95% confidence intervals (CI), as adjusted for other clinical factors.

Additionally, Kaplan–Meier survival analysis was performed to compare the cumulative probability of developing NTG progression (as defined by event-based GPA) between upper- and lower-half subgroups stratified by the extent of IOP fluctuation.

All of the statistical analyses were performed using R software (version 3.5.2) for statistics. P values <0.05 were considered statistically significant. The data ranges were recorded as mean ± standard deviations.

RESULTS

A total of 129 eyes of 129 subjects with NTG (64 eyes of 64 non-myopic NTG patients and 65 eyes of 65 myopic NTG patients) were included. The mean age at the initial visit was 60.2 ± 11.1 years, and 65 patients (50.4%) were female. The average follow-up period was 8.3 ± 2.9 years. The rate of progression in the aspects of MD and VFI slope was -0.29 ± 0.77 dB/year and -1.10 ± 1.91%/year, respectively. The average percentage reduction of IOP from the baseline was 12.8 ± 12.2% during the follow-up with topical medications. The mean IOP fluctuation was 1.6 ± 0.6 mmHg, and the age at the initial visit, sex distribution, proportion of NTG progressors, central corneal thickness (CCT), baseline MD and PSD did not significantly differ. The refractive error, axial length, and the MD slope showed significant inter-group differences. The subjects' clinical characteristics are summarized in Table 1. Among the IOP-related factors, only percentage of IOP reduction was significantly different between the two groups (P = 0.029).

A multiple regression model showed significant interactions of IOP fluctuation (β = -0.64, 95% CI [-1.03, -0.25], P = 0.002) with myopia on the MD slope (Table 2). The coefficient was negative, which meant that with the same increase of IOP fluctuation, the MD slope magnitude decreased more (i.e. the progression rate was faster) in myopic eyes than in non-myopic eyes. In the subgroup analysis, IOP fluctuation was significantly associated with the MD slope (β = -1.27 dB/year/mmHg, 95% CI[-2.10, -0.45], P = 0.003; adjusted for other clinical factors) in myopic NTG (Table 3), whereas no significant factor was found for non-myopic NTG (Supplementary Table S1). A scatterplot showing the different distributions of the MD slopes according to the IOP fluctuation in the non-myopic and myopic NTG groups is provided in Fig. 1.

To assess the collinearity between IOP-related factors, we made various multivariate models with the IOP-related factors which showed significant results in the univariate analysis. Only one IOP-related factor was used for each multivariate model. As result, only IOP fluctuation showed significant interaction with myopia (Table S3). Table S4 depicts the similar analysis for multivariate models in myopic NTG eyes, in which IOP fluctuation showed significant

influence for the rate of MD progression.

Similarly, a significant interaction of IOP fluctuation with myopia (β = -1.94, 95% CI [-3.67, -0.22], P = 0.024) on the VFI slope was observed (Table 4). In addition, the worse baseline MD was associated with rapid decrease of VFI (β = 0.07, 95% CI [0.01, 0.12], P = 0.024). In myopic NTG, IOP fluctuation and trough IOP were significantly associated with the VFI slope (β = -2.32%/year/mmHg, 95% CI [-4.51, -0.10], P = 0.011; β = -1.13%/year/mmHg, 95% CI [-2.16, -0.10], P = 0.032, respectively; Table 5), whereas no significant associated factors were found for non-myopic NTG (Supplementary Table S2).

Only IOP fluctuation showed significant interaction with myopia for the VFI slope (Table S5). In Table S6, only IOP fluctuation among the IOP-related factors showed significant influence for the rate of VFI progression.

A scatterplot showing the different distributions of the VFI slopes according to the IOP fluctuation in the two groups is provided in Fig. 2.

Kaplan–Meier survival analysis was performed to estimate and compare the cumulative probability of NTG progression between the upper tertile subgroup and the lower tertile subgroup, as stratified by IOP fluctuation (Fig. 3A). The cut-off values of IOP fluctuation were 1.65 mmHg (for upper tertile group) and 1.35 mmHg (lower tertile group). The upper subgroup showed a greater cumulative probability of NTG progression than the lower (P = 0.011; log-rank test). On the other hand, the cumulative progression probability did not significantly differ according to the presence of myopia (P = 0.073; log-rank test; Fig. 3B). Also, Fig. 4 shows the Kaplan-Meier survival plots analysis for nonmyopes (Fig. 4A) and myopes (Fig. 4B). In nonmyopes, the difference of cumulative NTG progression probability were statistically significant (P = 0.031). In myopic NTG group, the difference between the two subgroups showed only borderline significance (P = 0.046).

Table 1. Comparison of clinical characteristics between non-myopes and myopes

Group	Non-myopic NTG (N=64)	Myopic NTG (N=65)	P-value
Age (years)	60.8 ± 9.4	59.6 ± 12.7	0.543
Female (%)	37 (57.8%)	28 (43.1%)	0.134
Disc hemorrhage (%)	15 (23.4%)	14 (21.5%)	0.796
Follow-up time (years)	8.9 ± 3.0	7.7 ± 2.7	0.015
NTG progression (%)	22 (34.4%)	27 (41.5%)	0.511
VFI slope (%/year)	-0.81 ± 1.58	-1.39 ± 2.15	0.082
MD slope (dB/year)	-0.41 ± 0.57	-0.45 ± 0.91	0.020
Spherical equivalent (D)	0.8 ± 1.1	-3.3 ± 4.1	< 0.001
CCT (μm)	527.5 ± 36.1	536.8 ± 27.1	0.114
Axial length (mm)	23.2 ± 0.6	25.4 ± 1.5	< 0.001
Baseline MD (dB)	-5.2 ± 5.2	-6.0 ± 5.3	0.398
Baseline PSD (dB)	6.5 ± 5.0	7.5 ± 4.8	0.269
IOP without medication (mmHg)	14.0 ± 3.3	14.7 ± 4.0	0.259
IOP during treatment			
IOP with medication (mmHg)	12.4 ± 1.5	12.6 ± 1.8	0.481
Percentage of IOP reduction (%)	10.5 ± 11.7	15.1 ± 12.5	0.029
IOP fluctuation (mmHg)*	1.6 ± 0.6	1.6 ± 0.6	0.995
Peak IOP (mmHg)†	13.9 ± 2.4	13.9 ± 2.7	0.977
Trough IOP (mmHg)‡	10.1 ± 1.4	10.3 ± 1.6	0.513

IOP = intraocular pressure; NTG = normal-tension glaucoma; dB = decibels; D = diopters; CCT = central corneal thickness; MD = mean deviation; VFI = visual field index

* Standard deviation of IOP measurements taken during treatment.

† Maximal IOP during treatment.

‡ Minimal IOP during treatment.

Table 2. Predictors of slope of mean deviation

Factors	Univariate analysis			Multivariate analysis		
	β	95% CI	P	β	95% CI	P
Age, years	-0.01	(-0.02, 0.01)	0.408			
Female sex	-0.03	(-0.27, 0.27)	0.127	-0.069	(-0.32, 0.18)	0.581
Spherical equivalent (D)	0.018	(-0.02, 0.06)	0.328			
CCT (μm)	0.001	(-0.003, 0.01)	0.507			
Axial length (mm)	0.02	(-0.09, 0.12)	0.768			
Baseline MD (dB)	0.005	(-0.02, 0.03)	0.690			
Myopia	-0.31	(-0.58, -0.05)	0.021	0.33	(-0.05, 0.42)	0.235
Disc hemorrhage	-0.068	(-0.39, 0.25)	0.679			
IOP without medication (mmHg)	-0.03	(-0.07, 0.003)	0.073	0.03	(-0.08, 0.14)	0.570
IOP with medication (mmHg)	-0.09	(-0.17, -0.02)	0.019	-0.03	(-0.17, 0.11)	0.700
IOP fluctuation (mmHg)	-0.40	(-0.60, -0.20)	<0.001	-0.10	(-0.76, 0.56)	0.767
Percentage of IOP reduction (%)	-0.01	(-0.02, 0.01)	0.303			
Peak IOP (mmHg)	-0.08	(-0.13, -0.03)	0.001	-0.02	(-0.20, 0.17)	0.848
Trough IOP (mmHg)	-0.02	(-0.11, 0.07)	0.623			
Interaction with myopia*						
IOP with medication	-0.02	(-0.17, 0.13)	0.784			
IOP fluctuation	**-0.62**	**(-1.00, -0.24)**	**0.002**	**-0.64**	**(-1.03, -0.25)**	**0.002**
Percentage of IOP reduction	-0.014	(-0.036, 0.01)	0.205			
Peak IOP	-0.08	(-0.18, 0.02)	0.136	0.16	(-0.007, 0.33)	0.060
Trough IOP	0.057	(-0.12, -0.24)	0.531			

CI = confidence interval; CCT, central corneal thickness; IOP, intraocular pressure; MD = mean deviation

* The interaction effect existed when the effect of an independent variable on the slope of the mean deviation changed between the myopia and non-myopia groups.

Table 3. Predictors of slope of mean deviation of myopes

Factors	Univariate analysis			Multivariate analysis		
	β	95% CI	P	β	95% CI	P
Age, years	-0.01	(-0.03, 0.006)	0.205			
Female sex	0.08	(-0.38, 0.53)	0.741			
Spherical equivalent (D)	-0.012	(-0.07, 0.04)	0.655			
CCT (μm)	0.003	(-0.005, 0.01)	0.430			
Axial length (mm)	0.12	(-0.04, 0.28)	0.151	0.067	(-0.08, 0.22)	0.369
Baseline MD (dB)	-0.005	(-0.05, 0.04)	0.816			
Disc hemorrhage	-0.074	(-0.62, 0.47)	0.789			
IOP without medication (mmHg)	-0.04	(-0.10, 0.01)	0.118	0.019	(-0.05, 0.08)	0.569
IOP with medication (mmHg)	-0.10	(-0.22, 0.024)	0.114	-0.08	(-0.40, 0.23)	0.593
IOP fluctuation (mmHg)	**-0.70**	**(-1.01, -0.40)**	**<0.001**	**-1.27**	**(-2.10, -0.45)**	**0.003**
Percentage of IOP reduction (%)	-0.010	(-0.028, 0.01)	0.274			
Peak IOP (mmHg)	-0.12	(-0.20, -0.04)	0.005	0.18	(-0.15, 0.51)	0.282
Trough IOP (mmHg)	0.008	(-0.13, 0.15)	0.914			

CI = confidence interval; CCT, central corneal thickness; IOP, intraocular pressure; MD = mean deviation

Table S1. Predictors of slope of mean deviation of non-myopes

Factors	Univariate analysis			Multivariate analysis		
	β	95% CI	P	β	95% CI	P
Age, years	0.004	(-0.01, 0.02)	0.569			
Female sex	-0.18	(-0.47, 0.11)	0.216			
Spherical equivalent (D)	-0.035	(-0.17, 0.10)	0.605			
CCT (μm)	0.002	(-0.003, 0.01)	0.478			
Axial length (mm)	0.095	(-0.24, 0.43)	0.566			
Baseline MD (dB)	0.011	(-0.02, 0.04)	0.414			
Disc hemorrhage	-0.078	(-0.42, 0.26)	0.644			
IOP without medication (mmHg)	-0.007	(-0.05, 0.04)	0.743			
IOP with medication (mmHg)	-0.075	(-0.17, 0.02)	0.106	-0.07	(-0.22, 0.09)	0.411
IOP fluctuation (mmHg)	-0.08	(-0.31, 0.15)	0.488			
Percentage of IOP reduction (%)	0.004	(-0.008, 0.02)	0.497			
Peak IOP (mmHg)	-0.04	(-0.10, 0.02)	0.163	-0.007	(-0.11, 0.09)	0.884
Trough IOP (mmHg)	-0.05	(-0.15, 0.05)	0.344			

CI = confidence interval; CCT, central corneal thickness; IOP, intraocular pressure; MD = mean deviation

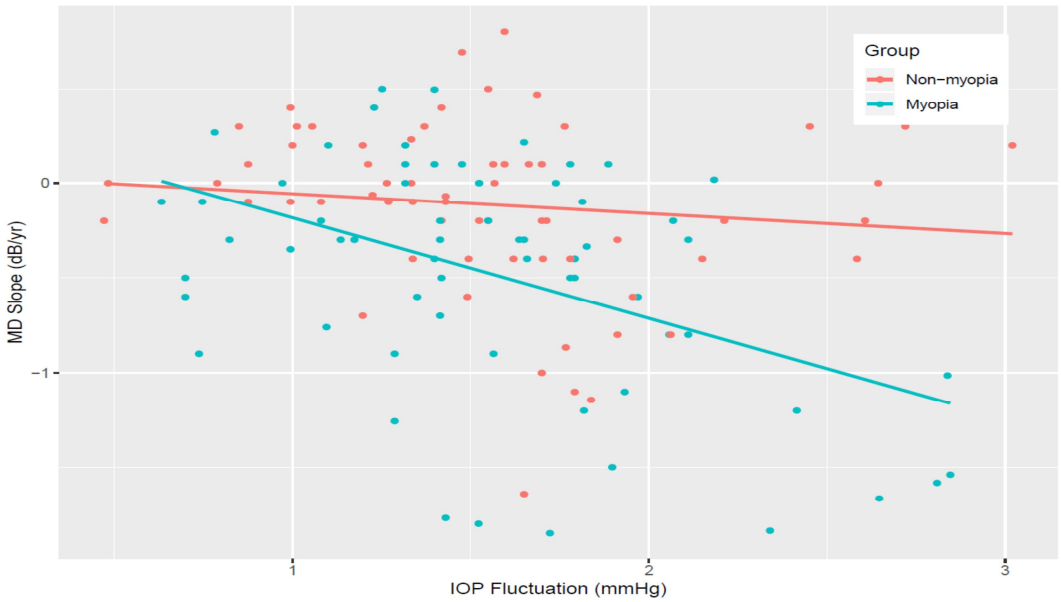

Fig. 1. Scatterplot and linear regression model showing correlation between IOP fluctuation and MD slope. In the myopia group, the MD slope decreased significantly with the increase of IOP fluctuation in the general linear model (β = -1.27, 95% confidence interval [-2.10, -0.45] dB/yr/mmHg, P = 0.003). In the non-myopia group, the MD slope and the IOP fluctuation were not significantly correlated. The difference of the correlation of the MD slope with the percentage IOP fluctuation was significant between the two groups (P = 0.002).

Table 4. Predictors of slope of visual field index (VFI)

Factors	Univariate analysis			Multivariate analysis		
	β	95% CI	P	β	95% CI	P
Age, years	-0.011	(-0.04, 0.019)	0.485			
Female sex	-0.25	(-0.91, 0.42)	0.461			
Spherical equivalent (D)	-0.004	(-0.10, 0.09)	0.941			
CCT (μm)	0.007	(-0.003, 0.018)	0.183			
Axial length (mm)	0.063	(-0.19, 0.32)	0.621			
Baseline MD (dB)	**0.053**	**(-0.01, 0.12)**	**0.096**	**0.07**	**(0.01, 0.12)**	**0.024**
Myopia	-0.58	(-1.23, 0.08)	0.078	0.43	(-4.10, 4.97)	0.850
Disc hemorrhage	-0.29	(-1.09, 0.50)	0.468			
IOP without medication (mmHg)	-0.15	(-0.23, -0.059)	0.001	-0.015	(-0.23, 0.30)	0.930
IOP with medication (mmHg)	-0.32	(-0.51, -0.13)	0.001	-0.13	(-0.75, 0.48)	0.446
IOP fluctuation (mmHg)	-1.04	(-1.54, -0.55)	<0.001	-0.91	(-2.54, 0.72)	0.270
Percentage of IOP reduction (%)	-0.027	(-0.05, 0.001)	0.053	-0.003	(-0.08, 0.07)	0.923
Peak IOP (mmHg)	-0.25	(-0.37, -0.12)	<0.001	0.243	(-0.27, 0.75)	0.344
Trough IOP (mmHg)	-0.19	(-0.40, 0.03)	0.096	-0.36	(-1.00, 0.28)	0.27
Interaction with Myopia*						
IOP with medication	-0.208	(-0.589, 0.174)	0.283			
IOP fluctuation	**-1.57**	**(-2.51, -0.63)**	**0.001**	**-1.94**	**(-3.67, -0.22)**	**0.024**
Percentage of IOP reduction	-0.060	(-0.11, -0.006)	0.030	-0.037	(-0.09, 0.01)	0.159
Peak IOP	-0.27	(-0.51, -0.02)	0.034	0.185	(-0.24, 0.61)	0.387
Trough IOP	-0.13	(-0.58, 0.31)	0.550			

CI = confidence interval; CCT, central corneal thickness; IOP, intraocular pressure; MD = mean deviation

* The interaction effect existed when the effect of an independent variable on the slope of the visual field index changed between the myopia and non-myopia groups.

Table 5. Predictors of slope of VFI of myopes

Factors	Univariate analysis			Multivariate analysis		
	β	95% CI	P	β	95% CI	P
Age, years	-0.037	(-0.08, 0.004)	0.076	-0.20	(-0.06, 0.02)	0.329
Female sex	-0.14	(-1.22, 0.95)	0.799			
Spherical equivalent (D)	-0.087	(-0.22, 0.05)	0.204			
CCT (μm)	0.016	(-0.004, 0.04)	0.101	0.005	(-0.01, 0.02)	0.588
Axial length (mm)	0.32	(-0.06, 0.70)	0.100	0.125	(-0.22, 0.47)	0.476
Baseline MD (dB)	0.063	(-0.04, 0.16)	0.216			
Disc hemorrhage	-0.35	(-1.65, 0.96)	0.597			
IOP without medication (mmHg)	-0.22	(-0.35, -0.10)	0.001	0.128	(-0.25, 0.50)	0.495
IOP with medication (mmHg)	-0.40	(-0.67, -0.12)	0.006	0.007	(-1.02, 1.03)	0.989
IOP fluctuation (mmHg)	**-1.80**	**(-2.51, -1.10)**	**<0.001**	**-2.32**	**(-4.51, -0.10)**	**0.011**
Percentage of IOP reduction (%)	-0.05	(-0.09, -0.01)	0.018	-0.05	(-0.16, 0.05)	0.285
Peak IOP (mmHg)	-0.36	(-0.54, -0.18)	<0.001	0.83	(-0.23, 1.89)	0.234
Trough IOP (mmHg)	**-0.23**	**(-0.56, 0.098)**	**0.165**	**-1.13**	**(-2.16, -0.10)**	**0.032**

CI = confidence interval; CCT, central corneal thickness; IOP, intraocular pressure; MD = mean deviation

Table S2. Predictors of slope of VFI of non-myopes

Factors	Univariate analysis			Multivariate analysis		
	β	95% CI	P	β	95% CI	P
Age, years	0.035	(-0.007, 0.08)	0.098	0.029	(-0.01, 0.07)	0.171
Female sex	-0.55	(-1.34, 0.24)	0.172	-0.46	(-1.25, 0.33)	0.250
Spherical equivalent (D)	-0.001	(-0.38, 0.38)	0.995			
CCT (μm)	0.004	(-0.008, 0.02)	0.481			
Axial length (mm)	-0.13	(-1.09, 0.83)	0.780			
Baseline MD (dB)	0.035	(-0.04, 0.11)	0.362			
Disc hemorrhage	-0.27	(-1.21, 0.66)	0.563			
IOP without medication (mmHg)	-0.02	(-0.14, 0.10)	0.705			
IOP with medication (mmHg)	-0.19	(-0.44, 0.07)	0.146	-0.158	(-0.41, 0.096)	0.218
IOP fluctuation (mmHg)	-0.23	(-0.87, 0.40)	0.468			
Percentage of IOP reduction (%)	0.009	(-0.03, 0.04)	0.592			
Peak IOP (mmHg)	-0.10	(-0.26, 0.06)	0.231			
Trough IOP (mmHg)	-0.10	(-0.38, 0.19)	0.496			

CI = confidence interval; CCT, central corneal thickness; IOP, intraocular pressure; MD = mean deviation

Table S3. Various multivariate linear regression models for the slope of mean deviation

Factors	Model 1*			Model 2†		
	B	**95% CI**	**P**	**β**	**95% CI**	**P**
Female sex	-0.05	(-0.33, 0.17)	0.518	-0.06	(-0.32, 0.20)	0.652
Myopia	0.70	(-0.30, 1.36)	0.231	0.96	(-0.61, 2.52)	0.230
IOP without medication (mmHg)	0.01	(-0.03, 0.05)	0.481	0.004	(-0.04, 0.05)	0.833
IOP with medication (mmHg)	-0.01	(-0.09, -0.08)	0.896	0.082	(-0.06, 0.23)	0.264
IOP fluctuation (mmHg)	-0.10	(-0.39, 0.19)	0.490			
Peak IOP (mmHg)				-0.085	(-0.19, 0.02)	0.118
Interaction with myopia						
IOP fluctuation	-0.64	(-1.02, -0.25)	0.0015			
Peak IOP				-0.085	(-0.188, 0.02)	0.102

CI = confidence interval; CCT, central corneal thickness; IOP, intraocular pressure; MD = mean deviation

* Peak IOP along with interaction with myopia was excluded for this analysis.

† IOP fluctuation along with interaction with myopia was excluded for this analysis.

Table S4. Various multivariate linear regression models for the slope of mean deviation of myopes

Factors	Model 1*			Model 2†		
	β	95% CI	P	β	95% CI	P
Axial length (mm)	0.06	(-0.08, 0.21)	0.401	0.08	(-0.08, 0.24)	0.332
IOP without medication (mmHg)	0.02	(-0.04, 0.09)	0.500	0.01	(-0.06, 0.08)	0.754
IOP with medication (mmHg)	0.06	(-0.04, 0.09)	0.404	0.213	(-0.05, 0.47)	0.113
IOP fluctuation (mmHg)	-0.89	(-1.34, -0.45)	<0.001			
Peak IOP (mmHg)				-0.26	(-0.45, 0.06)	0.110

CI = confidence interval; CCT, central corneal thickness; IOP, intraocular pressure; MD = mean deviation

* Peak IOP was excluded for this analysis.

† IOP fluctuation was excluded for this analysis.

Table S5. Various multivariate linear regression models for the slope of VFI

Factors	Model 1*			Model 2†			Model 3‡		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
Baseline MD (dB)	0.06	(0.005, 0.12)	0.034	0.06	(0.005, 0.13)	0.035	0.057	(-0.001, 0.12)	0.056
Myopia	1.93	(-0.29, 3.57)	0.061	0.483	(-1.27, 2.24)	0.587	3.11	(-0.66, 6.88)	0.105
IOP without medication (mmHg)	-0.04	(-0.14, 0.05)	0.373	-0.15	(-0.32, 0.02)	0.078	-0.06	(-0.16, 0.04)	0.236
IOP with medication (mmHg)	-0.21	(-0.64, 0.22)	0.341	-0.13	(-0.71, 0.46)	0.663	-0.15	(-0.72, 0.42)	0.604
IOP fluctuation (mmHg)	-0.42	(-1.56, 0.73)	0.472						
Percentage of IOP reduction (%)				-0.05	(-0.26, 0.15)	0.614			
Peak IOP (mmHg)							-0.07	(-0.34, 0.21)	0.625
Trough IOP (mmHg)	-0.32	(-0.94, 0.30)	0.306	-0.013	(-0.587, 0.561)	0.965	0.21	(-0.21, 0.63)	0.329
Interaction with Myopia*									
IOP fluctuation	-1.48	(-2.44, -0.52)	0.003						
Percentage of IOP reduction				-0.08	(-0.22, 0.07)	0.285			
Peak IOP							-0.24	(-0.48, 0.01)	0.059

CI = confidence interval; CCT, central corneal thickness; IOP, intraocular pressure; MD = mean deviation

* IOP fluctuation along with interaction with myopia was included for this analysis.
† Percentage of IOP reduction along with interaction with myopia was included for this analysis.
‡ Peak IOP along with interaction with myopia was included for this analysis.

Table S6. Various multivariate linear regression models for the slope of VFI of myopes

Factors	Model 1*			Model 2†			Model 3‡			Model 4§		
	β	95% CI	P	β	95% CI	P	β	95% CI	P	β	95% CI	P
Age, years	-0.02	(-0.06, 0.03)	0.466	-0.02	(-0.06, 0.02)	0.342	-0.02	(-0.06, 0.02)	0.315	-0.02	(-0.06, 0.02)	0.285
CCT (μm)	0.01	(-0.01, 0.03)	0.321	0.01	(-0.01, 0.03)	0.294	0.01	(-0.01, 0.03)	0.342	0.01	(-0.01, 0.03)	0.335
Axial length (mm)	0.14	(-0.21, 0.49)	0.443	0.11	(-0.26, 0.47)	0.560	0.15	(-0.21, 0.52)	0.402	0.17	(-0.20, 0.54)	0.355
IOP without medication (mmHg)	-0.06	(-0.22, 0.11)	0.494	-0.23	(-0.41, -0.05)	0.013	-0.08	(-0.26, 0.09)	0.343	-0.11	(-0.28, 0.06)	0.185
IOP with medication (mmHg)	-0.05	(-0.42, 0.32)	0.785	-0.09	(-0.46, 0.27)	0.610	0.12	(-0.49, 0.73)	0.695	-0.58	(-1.18, 0.02)	0.059
IOP fluctuation (mmHg)	-1.45	(-2.50, -0.40)	0.008									
Percentage of IOP reduction (%)				-0.05	(-0.16, 0.05)	0.285						
Peak IOP (mmHg)							-0.35	(-0.79, 0.09)	0.118			
Trough IOP (mmHg)										0.390	(-0.25, 1.03)	0.227

CI = confidence interval; CCT, central corneal thickness; IOP, intraocular pressure; MD = mean deviation

* IOP fluctuation was included for this analysis.
† Percentage of IOP reduction was included for this analysis.
‡ Peak IOP was included for this analysis.
§ Trough IOP was included for this analysis.

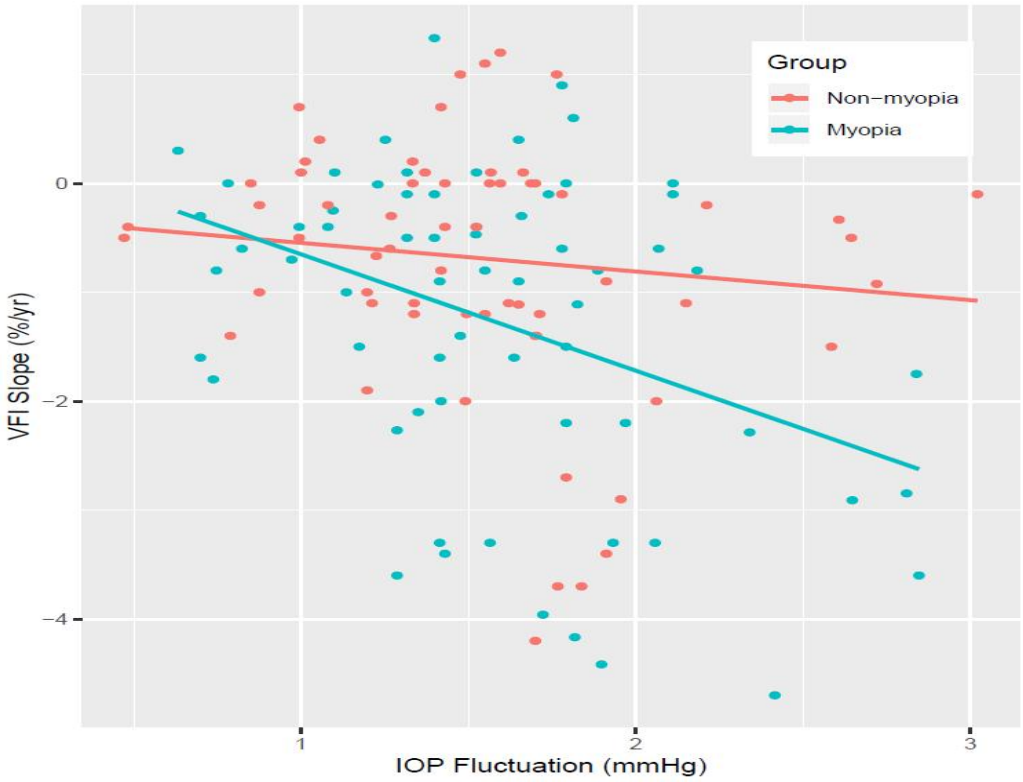

Fig. 2. Scatterplot and linear regression model showing correlation between IOP fluctuation and VFI slope. In the myopia group, the VFI slope decreased significantly with the increase of IOP fluctuation in the general linear model (β = -2.32, 95% confidence interval [-4.51, -0.10] %/year/mmHg, P = 0.011). In the non-myopia group, there was no significant correlation. The difference of the correlation of VFI slope with IOP fluctuation was significant between the two groups (P = 0.024).

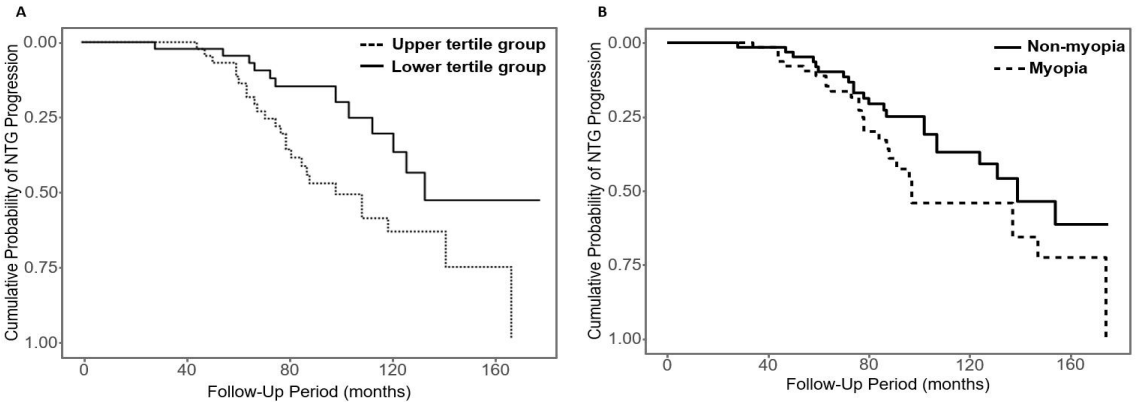

Fig. 3. Kaplan–Meier survival plot of normal-tension glaucoma (NTG) progression of study population as stratified by **(A)** intraocular pressure (IOP) fluctuation and **(B)** presence of myopia. NTG progression was defined by the event-based analysis using Guided Progression Analysis (GPA) software. IOP fluctuation was defined by the standard deviation of IOPs measured during treatment. **(A)** The cumulative probability of NTG progression in the upper tertile group (IOP fluctuation > 1.65 mmHg) and lower tertile group (IOP fluctuation < 1.35 mmHg) were significantly different (P = 0.011). **(B)** The cumulative probability of NTG progression in myopes and non-myopes did not significantly differ (P = 0.073).

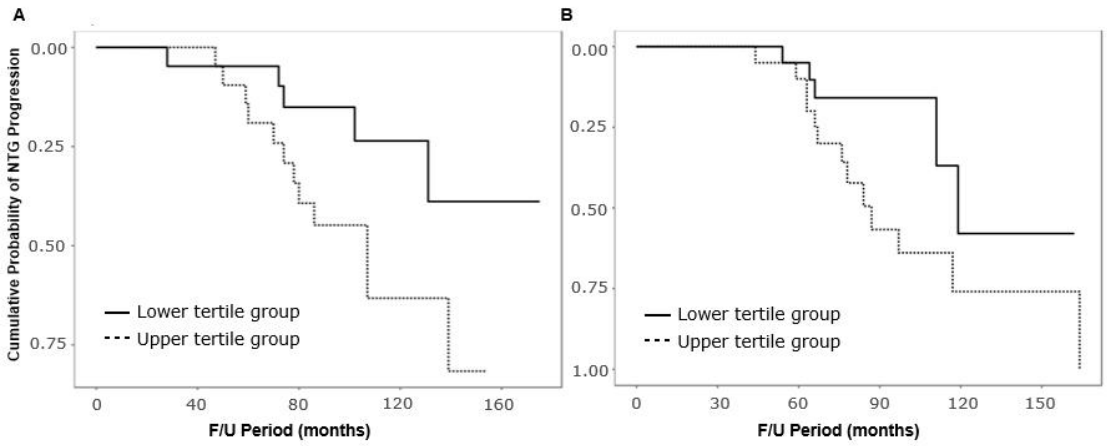

Fig. 4. Kaplan–Meier survival plot of normal-tension glaucoma (NTG) progression of study population as stratified by intraocular pressure (IOP) fluctuation in nonmyopes **(A)** and myopes **(B)**. **(A)** The cumulative probability of nonmyopic NTG progression in the upper tertile group and lower tertile group were significantly different (P = 0.031). **(B)** The difference of cumulative probability of myopic NTG progression between upper tertile and lower tertile groups showed borderline significance (P = 0.096).

DISCUSSION

In this study, we analyzed the impact of myopia on the association of IOP-related factors with the rate of NTG progression. Long-term IOP fluctuation was related to faster VF progression in myopic eyes, not in non-myopic eyes. The differences of the distribution patterns of the MD and VFI slope magnitudes between the 2 groups were significant.

There were several conflicting results in regard to the association of IOP fluctuation with glaucoma progression. Long-term IOP fluctuation was associated with a progressive increase in VF deterioration, even though patients with glaucoma maintained their IOPs after the triple procedure.[28] Also, a recent study on a Japanese NTG cohort with IOP ≤15mmHg without treatment showed that IOP fluctuation significantly contributed to progression.[29] The Advanced Glaucoma Intervention Study (AGIS) reported that long-term IOP fluctuations are associated with VF progression in patients with low mean IOP.[6] On the contrary, some reports, such as that of the EMGT, have argued that IOP fluctuation is not related to progression.[2, 3]

Progression rate as well as glaucoma progression itself is important in clinical practice, and associations with IOP fluctuation have been explored. A collaborative NTG study (CNTGS) reported a natural progression rate of untreated NTG of -0.39 dB/year,[30] while the EMGT reported -0.36 dB/year.[31] In treated patients, Fukuchi et al. found that fast progressors among NTG patients had a higher IOP fluctuation compared with slow progressors, which fact was not the case in HTG.[32] In contrast, Rao et al. noted that for each 1 mmHg increase in IOP fluctuation, progression worsened by 0.35%/year in HTG and angle-closure glaucoma. In our cohort, the mean progression rate was -0.29 ± 0.77 dB/year, and IOP fluctuation was not correlated to the rate of progression in the overall NTG patient group.

In the present study, we introduced an interaction-effect term to evaluate the impact of myopia on the relationship between the risk effect of IOP fluctuation and the rate of progression (linear regression).[33, 34] An interaction effect exists when the effect of an independent variable on a dependent variable changes according to the value of another independent variable. For the rate of progression in the current study, a significant interaction was observed, which means that

myopia modified the effect of IOP fluctuation. And indeed, the difference of the association was confirmed by our stratified analysis.

Myopic eyes are known to have a thinner lamina cribrosa (LC) and sclera than non-myopic eyes and to be more susceptible to glaucomatous damage.[20, 35] Asymmetrical structural changes in myopia between the superior and inferior LC can incur vulnerability to IOP even within the normal range.[36] Myopic thinning can make the LC more susceptible to deformation. As IOP fluctuation increases, the fluctuation of the translaminar pressure (TLP) difference might also increase. The thinner LC thickness of myopic eyes makes the variability of the TLP gradient greater than that for non-myopic eyes with the same TLP difference fluctuation. Furthermore, myopia is significantly associated with focal LC defects[37] that might induce more susceptibility to IOP fluctuation.

According to Kim et al.,[2] the percentage reduction of IOP and the occurrence of DH were associated with NTG progression risk. However, they were not significant predictors of the rate of progression. This discrepancy is difficult to explain to any degree of certainty, though we did formulate a hypothesis, which we will present as follows. In our study, the follow-up period was long (average: 8.2 years), and if the patient showed progression, the IOP-lowering treatment was escalated to prevent further progression. Moreover, eyes with DH, which were considered to be at elevated risk of progression, also tended to undergo more intensive treatment. Thus, the progression rate of the progressors during treatment was not as fast, and therefore too, the risk factors for progression could differ from the rate of progression. Also, in our cohort, the mean percentage of IOP reduction was lower than in previous studies. According to the CNTGS, a 30% IOP reduction significantly lowers the risk of progression;[4] however, a 30% reduction in IOP in NTG patients is not always achievable with topical medication.[38] Such different responses to IOP-lowering treatment could limit evaluations of the effect of IOP reduction on progression rate.

A previous study based on POAG (including both NTG and HTG) revealed that age at the initial visit was significantly related to the MD slope in glaucomatous eyes with myopia compared with eyes without myopia.[19] However, in the present study's univariate analysis, age was related

to the VFI slope magnitude with only borderline significance (β = -0.037, P = 0.076), which turned out not to be significant in the subsequent multiple linear regression analysis (β = -0.020, P = 0.329). The rate of MD deterioration in the myopic POAG was reported to -0.18 ± 1.55 dB/year previously,[19] which was slower than our result. However, the mean rate of change in the older myopic group (age >80 years) was -0.49 ± 1.77 dB/year, much faster than in the overall myopic POAG group. In our cohort, the mean age was younger, and only 2 of 65 patients (3.1%) were older than 80 years at the initial visit. Such a different age distribution could have affected the difference between 2 studies. Also, IOP fluctuation was not a significant predictor of MD slope in myopic POAG (baseline IOP: 19.82 ± 2.24 mmHg) according to Park et al.,[19] in contrast to our results. Although direct comparison of the two studies is difficult, the different types of glaucoma as well as the different distributions of baseline IOP without medication (NTG vs. POAG) might account for the discordances in the results.

There are a few previous studies on anti-glaucoma drugs' potency for long-term IOP fluctuation, though the issue has not yet been adequately understood for application to clinical practice. In one of those studies, glaucomatous eyes treated with bimatoprost demonstrated less long-term IOP fluctuation than did latanoprost-treated eyes.[39] Also, in another of those studies, patients treated with fixed-combination brimonidine-timolol were more likely to have low inter-visit IOP fluctuation than were patients treated with brimonidine or timolol alone, in a 12-month trial.[40] Additional studies are needed to reveal the potency decrease with IOP fluctuation over longer treatment periods, especially in myopic NTG. It would certainly be useful in enabling clinicians to choose more effective anti-glaucoma drugs for myopic NTG patients.

Our study had several limitations. First, the sample size was only modest, and the statistical power might have been too low to reveal the significant effects of some variables. For example, the association of age with the rate of progression might have been different if we had enrolled more patients in an older-age subgroup. Second, it is possible that patients who showed faster progression should have been excluded from this study due to glaucoma surgery or other additional treatments, which could have introduced selection bias into our analyses. Third, all the IOPs were measured within office hours, from 9 AM to 5 PM. However, peak IOP during

24-hour measurements has been reported to be almost 5 mm Hg higher than peak office IOP, and in fact, most glaucoma patients show their peak IOP values outside of office hours.[41] Recently, self rebound tonometry or 24-hour continuous IOP-related profile monitoring able to monitor the variability has become available,[42, 43] and further research into glaucoma progression with integration of information of 24-hour and long-term IOP fluctuation data would certainly be interesting.

In conclusion, long-term fluctuation of IOP was associated with MD and VFI progression rates in myopic NTG, but not also in non-myopic NTG. Additionally, worse baseline MD was associated with faster VFI deterioration. Long-term IOP fluctuation should be carefully monitored to prevent VF progression in myopic NTG patients.

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국문 초록

목적

정상안압녹내장에서 녹내장의 진행 속도와 장기 안압변동의 연관성에 근시가 영향을 주는지 여부를 조사하고자 한다.

방법

5 년 이상 국소 약물 치료를 받은 65 명의 근시 정상안압녹내장 환자들과(안축장 길이>24.0mm) 64 명의 비근시 정상안압녹내장 환자들(안축장 길이<24.0mm)의 의료 기록을 검토하였다. 평균 편차 기울기(mean deviation, MD), 시야 지수(visual field index, VIF)와 안압 관련 임상적 요인들과의 관계를 분석하기 위해 다중 선형 회귀 방식을 적용했다.

결과

평균 관찰 기간은 8.3 년이었다. 정상 안압 전체 환자에서 22 안(34.4%)의 비근시안과 27 안(41.5%)의 근시안에서 녹내장 진행을 보였다. 근시와 안압 변동과의 상호작용은 MD 및 VIF 기울기 (각각 P= 0.002, 0.024)와 관련하여 중요한 인자였다. 계층화된 분석은 안압 변동의 위험 효과가 MD 와 VFI 기울기 측면에서 근시 환자군에서만 의미가 있다고 제시했다.

결론

정상안압녹내장에서 근시는 비근시에 비해 녹내장 진행 속도와 관련이 있었다.

주요어 : 정상안압녹내장, 근시, 녹내장 진행, 장기 안압변동

학 번 : 2017-21713