Adherence to Drop Treatment in Glaucoma Patients and Its Relationship with Progression

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ABSTRACT

Purpose: To evaluate the adherence of glaucoma patients to eye drop therapy and determine the effects of treatment adherence on disease progression.

Materials and Methods: A total of 147 patients followed at Van Yüzüncü Yıl University Department of Ophthalmology, between March 2019 and June 2019 were included in the study. Patients were examined and asked questions. Patients underwent peripapillary retinal nerve fiber layer analysis via optical coherence tomography.

Results: It was found that 66% of the patients adhered to eye drop treatment. The most common reasons for non-adherence were forgetting (40%) and running out of eye drop (38%). Correct instillation technique was demonstrated by 59% of the patients. There was significantly less disease progression in adherent patients compared to non-adherent patients (p=0.002) and in patients with correct instillation technique compared to those without (p=0.001).

Conclusion: This study showed adherence to eye drop therapy was 66% among glaucoma patients and 59% of patients showed correct drop instillation technique. More progression was observed in patients with poor adherence and patients who did not instill drops correctly.

Keywords: Glaucoma, Eye drop adherence, Progression.

INTRODUCTION

Intraocular pressure (IOP) elevation is the main risk factor for the development and progression of glaucoma.[1-3] High IOP is also the only treatable parameter in glaucoma patients. Therefore, eye drops that lower IOP are the first-line treatment option in glaucoma patients.[4] Non-adherence to antiglaucoma eye drop therapy is among the potential causes of high IOP, disease progression, and blindness in glaucoma patients.[5,6]

As in all chronic diseases, adherence to drug therapy is one of the biggest challenges in the management of glaucoma. Non-adherence rates reported in the literature are highly variable, ranging from 50% to 80%.[7,8] Adherence to a drug regimen refers to the degree to which patients use the drugs prescribed by the doctor. Non-adherence can be defined as not using the prescribed drug at all, using the correct drug at inappropriate doses or intervals, or using the wrong drug.[9,10] Common barriers to drug adherence are adverse effects of the drug, the use of multiple drugs, not being adequately informed about the seriousness of the disease, and treatment costs. As with other patient-administered therapies, another important cause of adherence to eye drop therapy is incorrect instillation technique. [9,11,12]

In the present study, we evaluated glaucoma patients to determine the rate of adherence to eye drop therapy, the proportion of patients who instilled their eye drops correctly, and the impact of these factors on disease progression.

MATERIAL AND METHODS

This cross-sectional study was conducted between March and June 2019 in the Glaucoma Unit of Van Yüzüncü Yıl University Department of Ophthalmology. Ethical approval was obtained from the Noninterventional Clinical Research Ethics Committee in the Yüzüncü Yıl University

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Received: 20.05.2020
Accepted: 08.04.2021
Glo-Kat 2021; 16: 83-89
DOİ: 10.37844/glauc.cat.2021.16.14

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Rectorate. The study was conducted based on the principles of the Declaration of Helsinki. All patients were informed about the study and signed informed consent forms before participating.

In this study, questions about drop adherence were asked to the patients who were followed up in the glaucoma unit. The peripapillary retinal nerve fiber layer (RNFL) analyzes performed by OCT data on the patients' record were examined for progression. We evaluated whether there was an association between the progression and drop adherence.

The study included 147 patients who were diagnosed with early to moderate

glaucoma in the ophthalmology department, followed-up in the glaucoma unit, and used antiglaucoma eye drops for at least 1 year. Patient group consisted of random glaucoma patients who came to the control in glaucoma unit. The patients underwent a complete ophthalmologic examination. All patients underwent peripapillary RNFL analysis using optical coherence tomography (OCT) (Spectralis® OCT, Heidelberg Engineering GmbH, Heidelberg, Germany). Nowadays, peripapillary RNFL analysis with OCT are the most commonly used progression analysis methods especially for early to moderate glaucoma cases.[13-15] Progression was assessed by analyzing RNFL progression analysis reports. After the RNFL thickness measurements with OCT, the expected change according to age and the slope of the current change are statistically compared by the OCT device. And it is shown as a p value. A value of $p<0.05$ is considered significant. Changes in RNFL thickness with p values <0.05 in OCT device were accepted as progression. Patients with at least 4 visits and 2 years of follow-up on OCT measurements were included in the study. Global peripapillary RNFL thickness was considered in OCT measurement. Mean baseline and result, global peripapillary RNFL thicknesses and changes in OCT were calculated in progressive and non-progressive groups. Patients with cylindrical and spherical refractive error exceeding -3.00, peripapillary vitreous bands, posterior uveitis, epiretinal membrane, and age-related macular degeneration were not included in progression analysis. Patients with problems such as segmentation error, posterior vitreous detachment, and macular edema that may cause misinterpretation in OCT were excluded from the study.

Patients younger than 18 years of age, patients with severe mental problems precluding them from answering the study questions, patients with disease that can lead to forgetfulness (such as Alzheimer's, diabetes), patients with difficulty communicating, patients who had used eye drops for less than 1 year and advanced visual field loss (mean deviation < -12 dB) or threat to fixation; mean IOP greater than 30 mm Hg or any IOP greater than 35 mmHg in either eye; visual acuity less than 0.5 in either eye were excluded from the study (28 patients).

The ophthalmology resident on rotation in the glaucoma unit (H.Ö.) examined the patients and collected data by face-to-face interview. Questions asked during the interview covered demographic characteristics (age, education level, socioeconomic status), disease severity, prescribed medications and treatment regimen (which eye, dose schedule, treatment duration), family history of glaucoma, extent of patient's knowledge about glaucoma, adherence to eye drop therapy, and instillation technique used. The questions asked to the patients are given in Table 1.

Adherence to eye drop therapy was defined as having used the drops on schedule without skipping any doses for the last week, while patients who had missed at least two doses in the last week were considered non-adherent. The

Table 1: *The questions asked to patients.*

1-	What is your education? Illiterate Elementary/middle school High school/University
2-	What is your monthly income? Low ≤$290 Low-Middle $ 291-$550 Middle-High $551-$1100 High > $1100
3-	Do you know the severity of glaucoma?
4-	How many drops(bottle) do you use in each eye?
5-	How many years have you been using drops?
6-	Do you have any other glaucoma patient in the family?
7-	Do you use the drop yourself?
8-	Have you been informed about your disease?
9-	Did you skip any doses of your drop for the last week, if yes, How many doses did you skip? What was your reason for not dropping the drop? Forgetting Running out of eye drop Not having the eye drops with them Adverse effects of the eye drop Others
10-	Can you show me how you drip the drop into your eye?

patients' were asked about their reasons for non-adherence. During the interview, the same ophthalmologist observed each patient's instillation technique using provided artificial tears. Instilling the drop on the cornea or conjunctiva without contacting the eyelids was considered correct, whereas touching the drop to the lids or ocular surface was regarded as incorrect instillation. Clinical information such as glaucoma type and surgical history were recorded from the patients' medical records.

Data management and coding were performed in Microsoft Excel 2010.

Statistical Analysis:

SPSS Version 23 (IBM, USA) package software was used for statistical analyses. Descriptive statistical tests were used to evaluate age, gender, number of eye drops used, socioeconomic status, family history of glaucoma, education level, disease severity, eye drop adherence, barriers to eye drop adherence, proper instillation technique, and progression. Normality of data distribution was assessed with Kolmogorov–Smirnov test. Chi-square test was used to evaluate associations between eye drop adherence and instillation technique and disease progression. Logistic regression analysis was performed to evaluate the relationships between eye drop adherence and the patient's age and number of eye drops used. A p value <0.05 was considered statistically significant. Mann-Whitney U test was used to compare the groups with and without progression according to age and sex. Mann-Whitney U test was used to compare the mean global peripapillary RNFL thicknesses between the groups with and without progression.

RESULTS

A total of 147 glaucoma patients were interviewed for this study. Their mean age was 61.54 (21–85) years. There were 85 male patients (58%) and 62 female patients (42%). Over half of the patients were illiterate (57%), while 8% were either high school or university graduates. Monthly income was below $550 for 92% of the patients. Treatment duration was less than 5 years for 59% of the patients and over 15 years for 3% of the patients.

Drops were used bilaterally in 69% of the patients, and 17% had family history of glaucoma in a first-degree relative. The most common glaucoma type (72%) was primary open-angle glaucoma (POAG). Surgical history included trabeculectomy in 17 patients and peripheral iridotomy in 14 patients. Demographic and clinical characteristics of the patients are summarized in Table 2.

Table 2: *Demographic and clinical characteristics of the glaucoma patients.*

Gender	**n (%)**
Male	85 (58)
Female	62 (42)
Education	
Illiterate	83 (57)
Elementary/middle school	52 (35)
High school/University	12 (8)
Socioeconomic status	
Low (≤$290)	75 (51)
Low-middle ($291-$550)	61 (42)
Middle-high ($551-$1100)	11 (8)
High (>-$1100)	0
Duration of eye drop use	
<5 years	87 (59)
5-10 years	42 (29)
11-15 years	13 (9)
>15 years	5 (3)
Eyes treated	
One eye	102 (69)
Both eyes	45 (31)
Glaucoma in family	
Yes	25 (17)
No	122 (83)
Seriousness of the disease	
I know	53 (36)
I don't know	94 (64)
Informed	
Adequate	65 (44)
Inadequate	82 (56)
Glaucoma type	
POAG	106 (72)
CACG	19 (13)
NTG	6 (4)
Other	16 (11)
Surgical history	
Trabeculectomy	17 (12)
Iridotomy	14 (8)

POAG: Primary open-angle glaucoma, CACG: Chronic angle-closure glaucoma, NTG: Normal-tension glaucoma

Ninety-seven (66%) of the patients were classified as adherent to eye drop therapy while 50 (34%) were considered non-adherent. The most common reasons for non-adherence were forgetting (40%) and running out of eye drop (38%), followed by not having the eye drops with them (18%) and adverse effects of the eye drop (4%).

Forty-four (30 %) of the patients have been using one drop, 31 (21%) have been using two drops, 68 (46%) have been using three drops and 4 (3%) have been using four drops. No statistically significant correlation was found between adherence to eye drop therapy and number of eye drops or age (p>0.05). However, higher educational level was associated with better adherence (p=0.04).

In terms of eye drop administration, 132 patients (90%) instilled the eye drops themselves, while the other patients asked for assistance from another person when instilling their eye drops. Of the patients who self-administered, 78 (59%) demonstrated correct instillation technique and 54 (41%) missed the target area when applying.

Glaucoma progression analysis could be performed in 115 (78%) of 147 patients. Progression was observed in 56 (49%) of assessed patients, while the other 59 (51%) showed no progression. Evaluation of glaucoma progression based on adherence to eye drop therapy revealed significantly less progression among patients who were treatment adherent compared to those who were not (p=0.002) . Progression was seen in 38% of the patients who were adherence to eye drop therapy and in 68% who were not adherence to eye drop therapy. Similarly, evaluation of the relationship between progression and instillation technique showed that patients who instilled the drops correctly had significantly less progression than those who did not (p=0.001). Progression was seen in 36% of the patients who instilled the drops correctly, while in 67% who instilled incorrectly.

There was no statistically significant difference in age and sex between the groups with and without progression (p = 0.5, p = 0.4).

In the group with progression, baseline mean global peripapillary RNFL thickness was 84.03 ± 16.15µm and the result mean global peripapillary RNFL thickness was 74.9 ± 15.2 µm. This change was statistically significant (p=0.001). In the non-progression group, baseline mean global peripapillary RNFL thickness was 84.38 ± 18.09µm and the result mean global peripapillary RNFL thickness was 84.88 ± 17.7µm. This change was not statistically significant (p=0.63)

When RNFL thickness change was calculated as µ ⁄ year, the change was -2.3 ± 1.7 in the progression group (p<0.001) and 0.2 ± 1.1 in the non-progression group (p>0.05). Clinical features of patients with and without progression are shown in Table 3. Sectoral peripapillary RNFL thickness of patients with and without progression are shown in Table 4. In the group with progression, a statistically significant difference was found between basal and final values in all sectoral quadrants.

DISCUSSION

Adherence to antiglaucoma drugs has varied in numerous studies. In a study by Rajurkar et al. conducted in northern India, the rate of non-adherence to antiglaucoma drugs was 49%.[16] Rates of non-adherence were also reported as 29% in Israel, 76% in Taiwan, and 19% in Saudi Arabia.[17,18,5] In a multicenter study conducted in Canada by Kholdebarin et al., the non-adherence rate was reported as 28%.[19] In a study conducted by Wolfram et al. in Germany, drug non-adherence was shown as 30.3%.[20] In another study in Brazil, drug non-adherence was reported as 40%.[21] Of the few studies on this subject conducted in Turkey, Çetin et al. reported a 24% non-adherence rate.[22] In our study, 34% of the patients were non-adherent. There are many reasons behind the high variability in treatment adherence rates. While differences between countries and regions in development level, socioeconomic level, and culture are some factors, another major factor is the lack of a standard definition of non-adherence. For instance, in the study by Kholdebarin et al., non-adherence was defined as missing a drop at least once a week and/or not following the drug regimen properly.[19] However, in another study, non-adherence was classified as partial and complete, with partial non-adherence defined as missing a drop at least once in the last week and complete non-adherence defined

Table 3: *Clinical features of patients with and without progression.*

	Progressors	Nonprogressors	P Value
Eyes (n)	56	51	
Age (years)	57.2±14.3	54.3±17.4	0.5
Baseline RNFL thickness (µm)	84.03±16.15	84.38±18.09	0.63
Progression Rates of RNFL thickness (µm⁄ year)	-2.3±1.7	0.2±1.1	**<0.001***

RNFL: Retinal nerve fiber layer, *Statistically significant value

Table 4: *Sectoral peripapillary RNFL values of patients with and without progression.*

	Progressors			Nonprogressors		
	Mean (µm)	**Std. Deviation**	**P value**	**Mean (µm)**	**Std. Deviation**	**P value**
Baseline NS	96.95	27.4	**<0.001**	85.96	25.6	0.41
Final NS	86.86	26.4		87.05	24.5	
Baseline N	70.04	16.9	**<0.001**	65.06	18.8	0.49
Final N	62.27	17.6		65.81	19.9	
Baseline NI	91.80	28.7	**<0.001**	87.9	30.3	0.27
Final NI	82.33	30.9		86.2	29.1	
Baseline TI	107.23	33.4	**<0.001**	98.05	31.8	0.99
Final TI	97.57	31.5		98.06	34.9	
Baseline T	65.16	17.1	**<0.001**	62.37	17.4	0.53
Final T	59.48	14.9		63.23	16.6	
Baseline TS	104.37	28.7	**<0.001**	99.03	35.3	0.93
Final TS	95.37	27.6		99.1	31.5	

NS: Nasal superior, N: Nasal, NI: Nasal inferior, TI: Temporal inferior, T: Temporal, TS: Temporal superior, RNFL: Retinal nerve fiber layer, Std: Standart.

as not instilling the drug at all in the last week.[16] In our study, we defined non-adherence as skipping at least two scheduled drops within the last week.

The most common reasons for non-adherence cited by participants in our study were forgetting, followed by running out of drops, not having the eye drop with them, and experiencing adverse effects of the eye drop. We also demonstrated an inverse relationship between education level and non-adherence. Similar to our results, Lacey et al. reported that although it varied between individuals, the main factors in non-adherence were low education, lack of motivation, and forgetfulness.[23] In another study, forgetfulness, high cost of drugs, and low education level were cited as reasons for non-adherence.[24] In a multicenter study by Ramin et al. including 500 patients, the most common causes of non-adherence were reported as forgetfulness and not having the eye drop with them.[19] In a study conducted by Musa et al., the most common reason for drug non-compliance was found to be forgetfulness (64.5%).[25]

Different studies have also shown that drug non-adherence is associated with patients not being adequately informed about the disease and doctors not emphasizing the significance of the disease enough. Masoud et al. reported that not having adequate information about the disease was the cause of drug non-adherence in 32% of cases, while underestimating the seriousness of the disease was the cause in 26% of cases.[6] In another study, two major causes of drug non-adherence were patient-doctor relationship and the doctor not mentioning the fact that glaucoma can lead to blindness.[26] Gelb et al. discussed the importance of patient-doctor communication and the doctor's view on this subject in terms of drug adherence.[27] In our study, 64% (n=94) of our patients stated that they did not have adequate knowledge about the disease, while 56% (n=82) stated that they were not adequately informed by their doctors about the disease.

Eye drop instillation technique is important for glaucoma patients to receive the required dose. In a study involving observation of 70 patients, only 6 patients instilled the eye drop properly, while the other patients either missed the eye or caused the drop to contact the eyelids.[9] Dietlein et al. determined that 68% of glaucoma patients successfully applied the drop to the cornea or conjunctiva, while in another study, Hosoda et al. found this rate to be 55%.[28,29] Correct instillation was observed in 59% of the patients in our study, similar to the values reported in the literature. Contamination of the drop upon contact with the ocular and adnexal structures due to incorrect installation is an important problem in terms of infection. A contamination rate of 80% was reported by Brown et al., while Kass et al. found this rate to be 50%.[30,31]

Treatment adherence and correct eye drop instillation are important in glaucoma patients due to the possibility of affecting disease progression. Few previous studies have examined the relationship between eye drop adherence

and progression. Konstas et al. compared adherent and non-adherent patients in terms of visual field loss and demonstrated greater losses in the non-adherent patients.[32] However, a relationship between visual field loss and poor eye drop adherence could not be detected in other studies that monitored progression based on visual field. [33,34] In our study, glaucoma progression was evaluated using OCT RNFL progression analysis reports, and it was found that adherent patients had significantly less progression compared to non-adherent patients (p=0.002). Similarly, we determined that patients who correctly instilled eye drops had significantly less progression compared to those with poor technique (p=0.001).

Our study has certain limitations. One of these is that the patients were questioned by their regular doctor. In this situation, the patient may hide their drug non-adherence from their doctor. Another limitation is that the study was conducted only among patients followed in the glaucoma unit. Visual field progression analysis of patients requires at least 3 visual field analysis. However, progression analysis with visual field was not used in the study due to the lack of visual field testing in most patients (noncompliance of the patients). This is another limitation of the study. In future studies, patients who were diagnosed but did not attend follow-up visits at the hospital could be contacted and included. In addition, future studies using combined OCT and visual field analyses for progression may yield more valuable data.

In conclusion, glaucoma is a chronic disease that preferentially affects older adults and requires long-term eye drop therapy. Therefore, eye drop non-adherence is common among glaucoma patients. Disease progression may be observed even in patients who use eye drops. Poor eye drop adherence and instillation technique may be a contributing factor to progression in patients using eye drops. There are many barriers to treatment adherence other than age. For this reason, most of those barriers can be eliminated through effective patient-doctor communication. Especially with patients who were recently diagnosed and started on eye drop therapy, the patient and at least one of their relatives should be provided detailed information about the seriousness of the disease, with emphasis on its potential to progress and cause blindness if not treated appropriately. In addition, patients and relatives should be shown how to correctly instill eye drops. These steps may increase patient adherence to eye drop therapy.

Acknowledgement

The authors declared that this study has received no financial support.

Declaration of Interest

The authors report no declarations of interest.

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