e-ISSN: 0975-1556, p-ISSN:2820-2643
Available online on www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2024; 16(11); 1282-1289

Original Research Article

Effect of Topical Antiglaucoma Drugs on Corneal Thickness

Haziqa Zahoor[1], Rakshan Reyaz[2], Asif Amin Vakil[3]

[1]Senior Resident, Department of Ophthalmology, GMC Srinagar, J&K
[2]Senior Resident, Department of Ophthalmology, GMC Srinagar, J&K
[3]Associate Professor, Department of Ophthalmology, GMC Srinagar, J&K

Received: 25-08-2024 / Revised: 23-09-2024 / Accepted: 28-10-2024
Corresponding Author: Dr Rakshan Reyaz
Conflict of interest: Nil

Abstract:

Purpose: To study the effect of topical antiglaucoma drugs on corneal thickness.

Material and Methods: A total of 108 eyes of 60 glaucoma patients who used topical antiglaucoma medications for a minimum period of 6 months were enrolled and followed up for a period of 1 year. Duration of therapy and drops/day were noted. Patients underwent complete ocular examination including ocular coherence tomography (OCT) for measurement of Corneal Epithelial Thickness (CET) and Central Corneal Thickness (CCT).

Results: The mean age of the patients was 55 ± 11.84 yrs. Corneal Epithelial Thickness (CET) had a baseline mean value of 60.02 ± 6.04µm which decreased to a mean value of 57.62 ± 6.16µm at 1 year follow up. Central Corneal Thickness (CCT) had a baseline value of 529.97 ± 40.8µm which decreased to a mean value of 524.56 ± 41.2µm at 1 year follow up. CET and CCT values decreased with increasing the number of drugs used and daily drops instilled.

Conclusion: CET and CCT values decreased over the one-year study period. Further, the values were found to be worsened with increasing the number of drugs used and daily drops instilled. The value worsened with increasing the number and frequency of drug instillation. The usage of preservative-free products, combination drug products, and concurrent use of lubricating eye drops may be helpful in slowing the damage on the corneal epithelium.

Keywords: Glaucoma, Cornea, antiglaucoma drugs, cet, cct, oct.

Introduction

Glaucoma is a chronic, progressive optic neuropathy caused by a group of ocular conditions, which lead to damage of the optic nerve with loss of visual function. [1] The most common risk factor known is raised intraocular pressure. Other risk factors include age, African ethnic background, family history of glaucoma, low central corneal thickness, trauma, long-standing ocular inflammation, prolonged steroid use, oral contraceptive intake, systemic conditions like diabetes, hypertension, asthma, heart failure, peripheral vascular disease, migraine, and coronary artery disease. [2,3]

Glaucoma is the second leading cause of visual impairment and blindness in the world. According to Quigley and Broman, there will be 60.5 million people with OAG and ACG in 2010, increasing to 79.6 million by 2020. [4,5]

The aim of glaucoma therapy is to preserve visual function with minimal complications. Treatment of glaucoma which revolves around reducing the intraocular pressure should be instituted as soon as a definite diagnosis of glaucoma is reached. [6]

Medical treatment of glaucoma is conventionally the first modality of treatment and includes the use of drugs like Cholinergic agonists, Adrenergic agonists, β Blockers, Carbonic Anhydrase inhibitors, Prostaglandin analogs, and Hyperosmotic agents. These drugs are invaluable in the management of glaucoma but are associated with certain adverse effects. [7]

The cornea represents one of the most altered tissues due to glaucomatous treatment, with changes involving all epithelial layers, stroma and endothelium. [8,9] The corneal epithelium exposed to toxic conditions, due to chronic glaucoma therapy, shows cellular changes and inflammatory infiltration that may lead to alteration of its role in the corneal tropism and ocular surface homeostasis. [9,10,11]

Corneal thickness is an important and sensitive indicator of corneal health. Lower Central Corneal Thickness (CCT) is a significant risk factor for the progression of ocular hypertension to primary open angle glaucoma (POAG), thus an important parameter in the risk profiling of ocular hypertensives and glaucoma patients. [12] It affects

the accuracy of intraocular pressure measurements. Damage to the ocular surface is evaluated based on Corneal Epithelial Thickness (CET). It is important to study the CET in patients with glaucoma because their modifications are associated with the development of ocular surface disease consequent to prolonged use of glaucoma therapy. [13,14,15]

The use of Optical Coherence Tomography (OCT) in measuring CET and CCT in comparison to previous techniques like high-frequency ultrasound and confocal microscopy has the advantage of being aseptic and without the risk of contact corneal trauma.[16,17,18] It is an objective method of evaluation and comparison as compared to older subjective methods like the Ocular Surface Disease Index (OSDI). Histologic ex vivo techniques, such as brush cytology or impression cytology have the drawback of being invasive. A further advantage of OCT is that it is possible to examine the results at a later time in the absence of the patient, hence the results are reproducible. [19,20,21]

Anterior Segment Optical Coherence Tomography (AS-OCT) is a non-contact and non-invasive imaging technique that captures high resolution cross-sectional images of the anterior eye segment. [9,14,22] OCT works on the principle of Low Coherence Interferometry. Light is sent along two optical paths, one being the sample path and other the reference path of the interferometer. The light source is an 840nm super luminescent light-emitting diode. Multiple interference patterns are created over the surface of the structure being imaged. As the instrument scans, a series of A-Scans is created. These A-scans are combined into a composite cross-sectional image (B-Scan). The most advanced AS-OCT systems use Fourier spectral-domain (SD-OCT) processing offering a higher speed and increased resolution compared with that of time-domain optical coherence tomography (TD OCT). [23,24]

The purpose of the study was to study the changes in the Corneal Epithelial Thickness and Central Corneal Thickness in patients using topical antiglaucoma medication. We also evaluated number of drugs and number of drops/day that may affect the ocular surface.

Materials and Methods:

Study Design: This was a hospital-based, prospective, observational study which was conducted over a period of one year. The study was undertaken after obtaining clearance from the Institutional Ethical Committee.

Patients: Diagnosed cases of POAG belonging to the age group 18 years and older, using one or more antiglaucoma medication for at least 6 months were included in the study. Patients who were excluded from the study were patients with secondary forms of glaucoma such as uveitic, neovascular or steroid induced glaucoma, systemic diseases affecting the ocular surface (e.g collagen vascular diseases, Wilson disease, Mucopolysaccharidoses, Fabry's disease.), any acute disease affecting the cornea (e.g ulcer, keratitis), any previous ocular surgery or trauma, use of contact lenses, patients with a history of Ocular Surface Disease (OSD), patients with blinking abnormality (e.g Parkinson Disease, Facial Nerve Palsy), patients using drugs e.g Antidepressants, Antihistaminics, Corticosteroids, Birth control pills.

After explaining the purpose and procedure of the study an informed consent of the patient was taken. Demographic information, medical and surgical history, medication usage, occupational history, personal history was taken. For ophthalmic history, the following parameters were recorded regarding topical medication use: number of IOP lowering medication, total duration of treatment, and the total number of drug instillations per day.

Patients underwent a complete ophthalmological examination including best-corrected visual acuity (BCVA), Slit Lamp examination, IOP determination, Gonioscopy, and Fundus examination.

Study procedures and outcome measures:

The corneal changes were studied using Cirrus High Definition OCT for measurement of Corneal Epithelial Thickness (CET) and Central Corneal Thickness (CCT).

Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA,USA) was used to obtain high-resolution anterior segments cans. Scans with a signal strength of $\geqslant 8$ were used for analysis. Scans with misalignment, poor illumination, or poor focus were excluded. CCT and CET were measured manually using the cursor provided by the AS-OCT software. The cursors were placed perpendicular to the ocular surface epithelium from a point located just beneath the tear film (first hyperreflective layer) to the Bowman Membrane (second hyperreflective layer). CCT and CET were measured manually by one examiner in five different places of each scan and the average value was calculated.

Statistical Analysis: The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Statistical software SPSS (version 20.0) and Microsoft Excel were used to carry out the statistical analysis of data. Continuous variables were expressed as Mean±SD and categorical variables were summarized as percentages. Paired t-test was employed to compare various parameters between baseline and one year follow-up. Graphically the data was presented by bar and pie diagrams. A P-

value of less than 0.05 was considered statistically significant.

Results

A total of 108 eyes of 60 patients (35 males and 25 females) with a mean age of 55.7±11.84 yrs who met the inclusion criteria participated in the study. The patients had the disease for a mean duration of 39.5±22.02 months.

Corneal Epithelial Thickness (CET) had a baseline mean value of 60.02 ± 6.04µm which decreased to a mean value of 57.62 ± 6.16µm at 1 year follow up (Table 1). The comparison between CET values and the number of drugs used by patients showed that patients using 1 drug had a difference of 2.04 µm between the baseline and 1-year follow-up values. The difference was 2.25 µm, 2.68 µm, and 2.86 µm in patients using 2,3 and 4 drugs respectively (Table 2). The comparison between CET values and the number of daily drops used by patients revealed that patients using 1-2 drops had a difference of 2.13 µm between the baseline and 1-year follow-up values. The difference was 2.56 µm and 2.64 µm in patients using 3-4 and 5-6 daily drug drops respectively (Table 3).

Central Corneal Thickness (CCT) had a baseline value of 529.97 ± 40.8µm which decreased to a mean value of 524.56 ± 41.2µm at 1 year follow up (Table 4). The comparison between CCT values and the number of drugs used by patients showed that patients using 1 drug had a difference of 5.17 µm between the baseline and 1-year follow-up values. The difference was 5.22 µm, 5.65 µm, and 6.02 µm in patients using 2,3 and 4 drugs respectively (Table 5). The comparison between CCT values and the number of daily drops used by patients revealed that patients using 1-2 drops had a difference of 4.11 µm between the baseline and 1-year follow-up values. The difference was 4.71 µm and 5.50 µm in patients using 3-4 and 5-6 daily drug drops respectively (Table 6).

Table 1: Corneal Epithelial Thickness at baseline and one-year follow-up in study eyes

Corneal Epithelial Thickness (µm)	Mean	SD	Difference	t-value	P-value
Baseline	60.02	6.04	2.40	32.26	<0.001*
At 1 year follow-up	57.62	6.16			

***Statistically significant difference with respect to baseline (P-value<0.05); P-value by paired t-test**

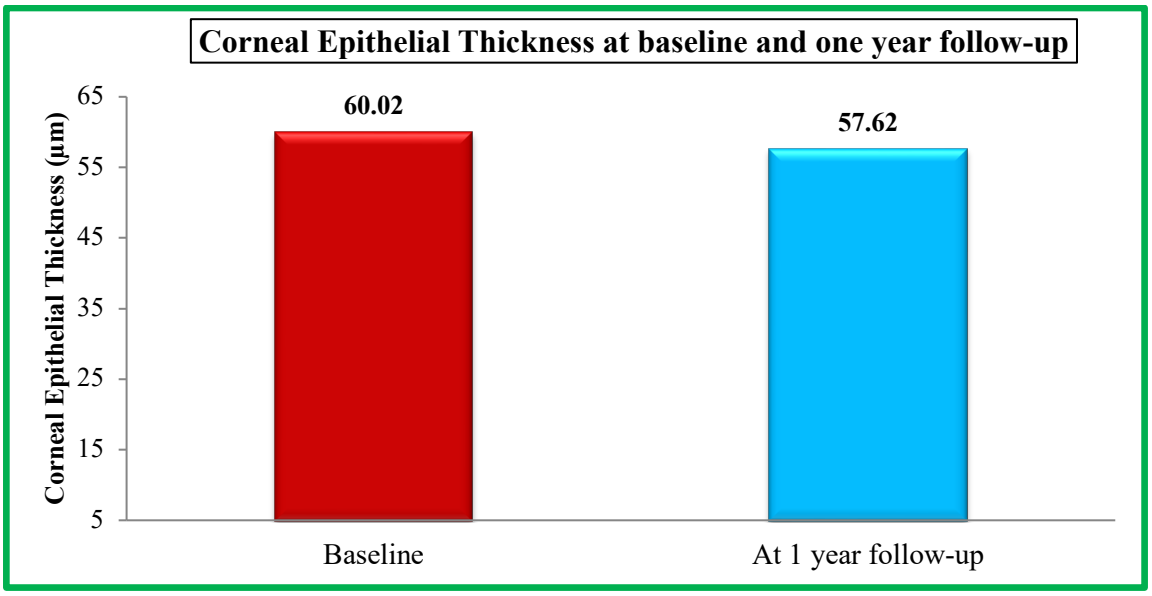


Table 2: Corneal Epithelial Thickness as per the number of drugs used at baseline and one-year follow-up

Number of drugs used	Baseline		At 1 year follow-up		Difference	t-value	P-value
	Mean	SD	Mean	SD			
1 Drug	60.74	5.86	58.70	6.03	2.04	15.36	<0.001*
2 Drugs	60.31	5.67	58.06	5.68	2.25	16.70	<0.001*
3 Drugs	58.70	6.28	56.03	6.26	2.68	19.89	<0.001*
4 Drugs	61.44	6.46	58.58	6.80	2.86	16.29	<0.001*

***Statistically significant difference with respect to baseline (P-value<0.05); P-value by paired t-test**

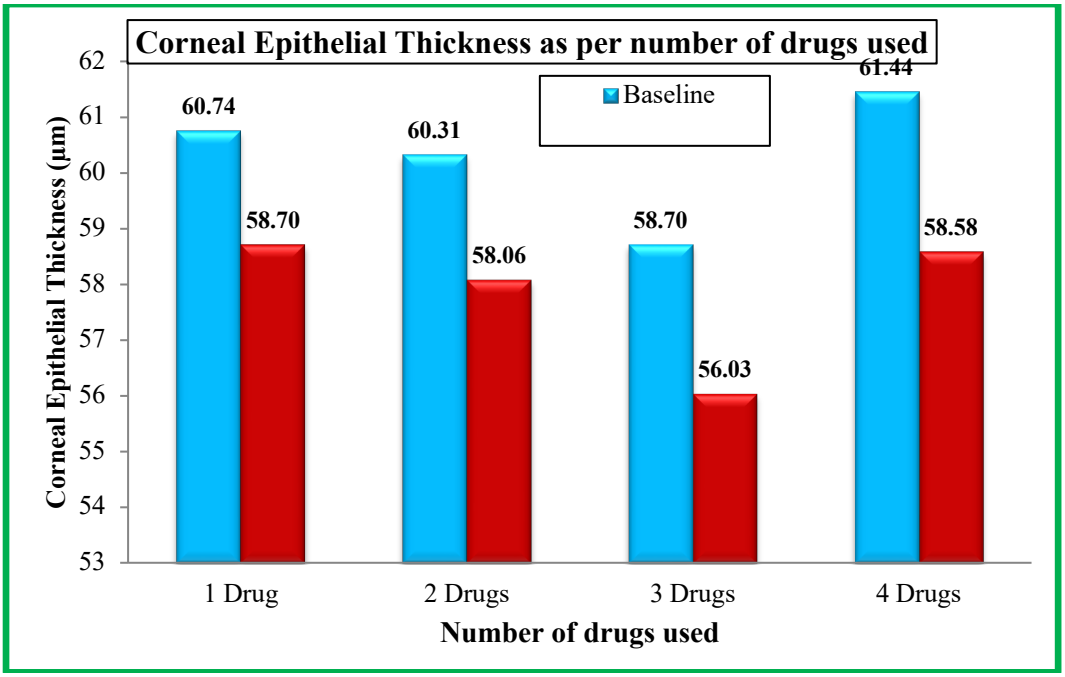


Table 3: Corneal Epithelial Thickness as per the number of daily drops at baseline and one-year follow-up

Number of daily drops	Baseline		At 1 year follow-up		Difference	t-value	P-value
	Mean	SD	Mean	SD			
1-2 Drops	60.78	5.69	58.64	5.74	2.13	18.91	<0.001*
3-4 Drops	59.12	6.25	56.56	6.27	2.56	21.13	<0.001*
5-6 Drops	60.14	6.40	57.50	6.71	2.64	18.79	<0.001*

***Statistically significant difference with respect to baseline (P-value<0.05); P-value by paired t-test**

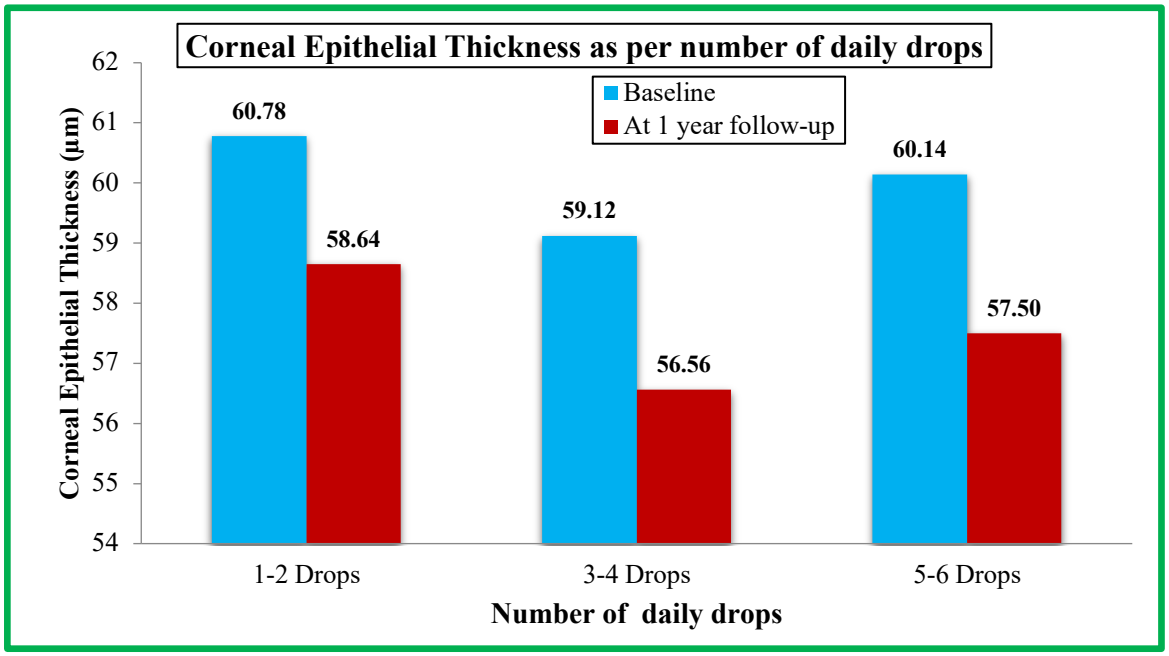


Table 4: Central Corneal Thickness (CCT) at baseline and one-year follow-up in study eyes

CCT (µm)	Mean	SD	Difference	t-value	P-value
Baseline	529.97	40.8	5.42	34.29	<0.001*
At 1 year follow-up	524.56	41.2			

***Statistically significant difference with respect to baseline (P-value<0.05); P-value by paired t-test**

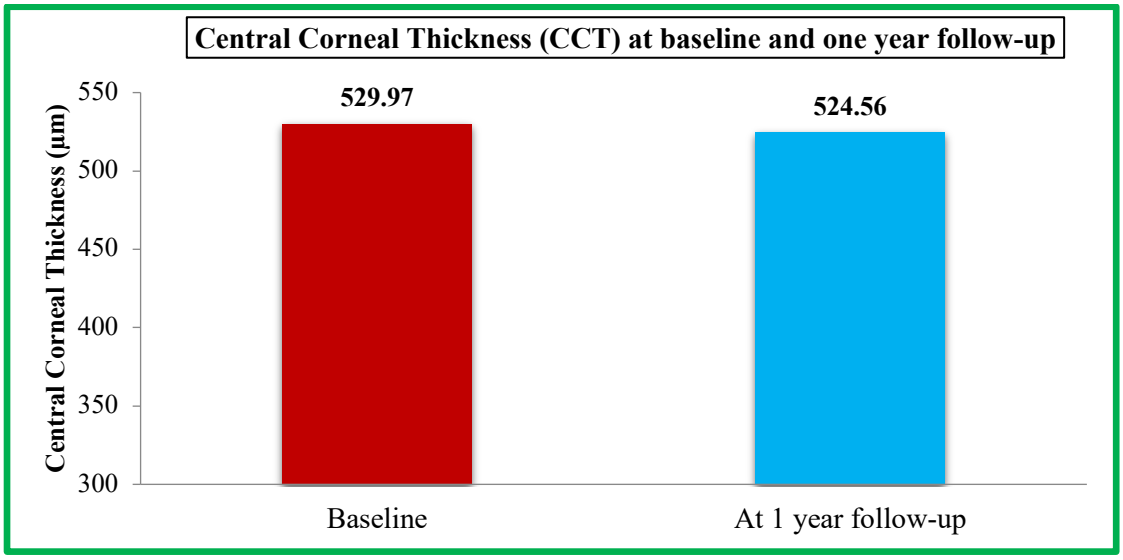


Table 5: Central Corneal Thickness (CCT) as per the number of drugs used at baseline and one-year follow-up

Number of drugs used	Baseline		At 1 year follow-up		Difference	t-value	P-value
	Mean	SD	Mean	SD			
1 Drug	533.04	33.15	527.87	33.50	5.17	19.06	<0.001*
2 Drugs	540.91	44.53	535.69	45.05	5.22	17.00	<0.001*
3 Drugs	510.92	35.82	505.27	36.03	5.65	20.99	<0.001*
4 Drugs	547.75	39.65	541.73	40.08	6.02	11.67	<0.001*

***Statistically significant difference with respect to baseline (P-value<0.05); P-value by paired t-test**

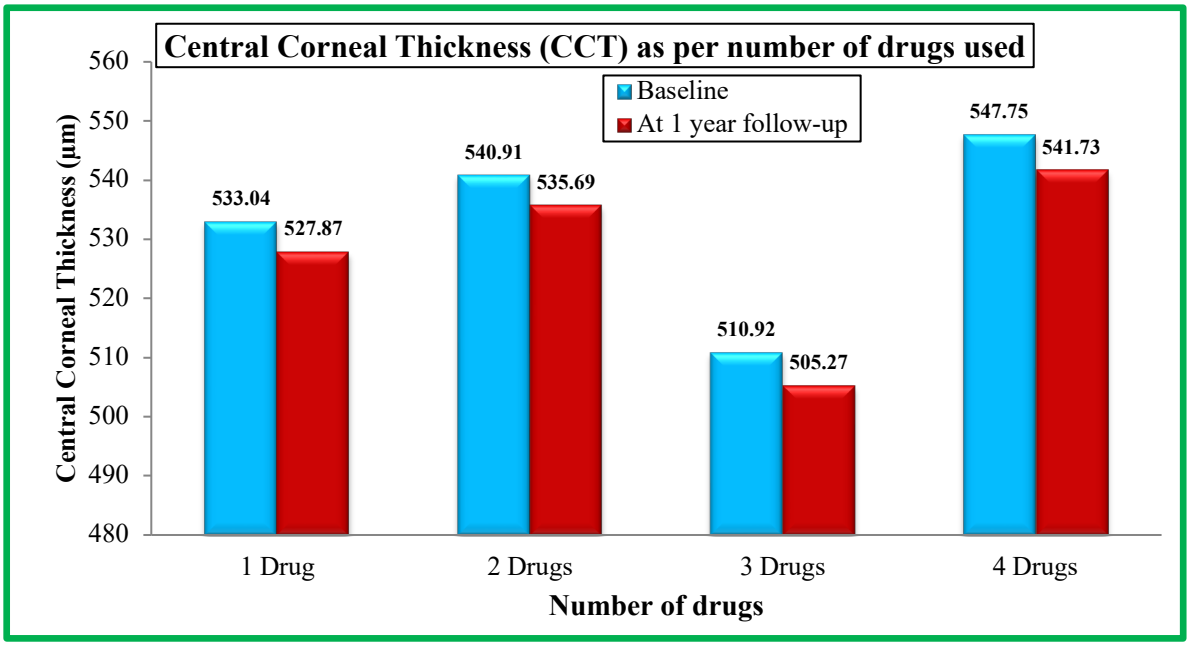
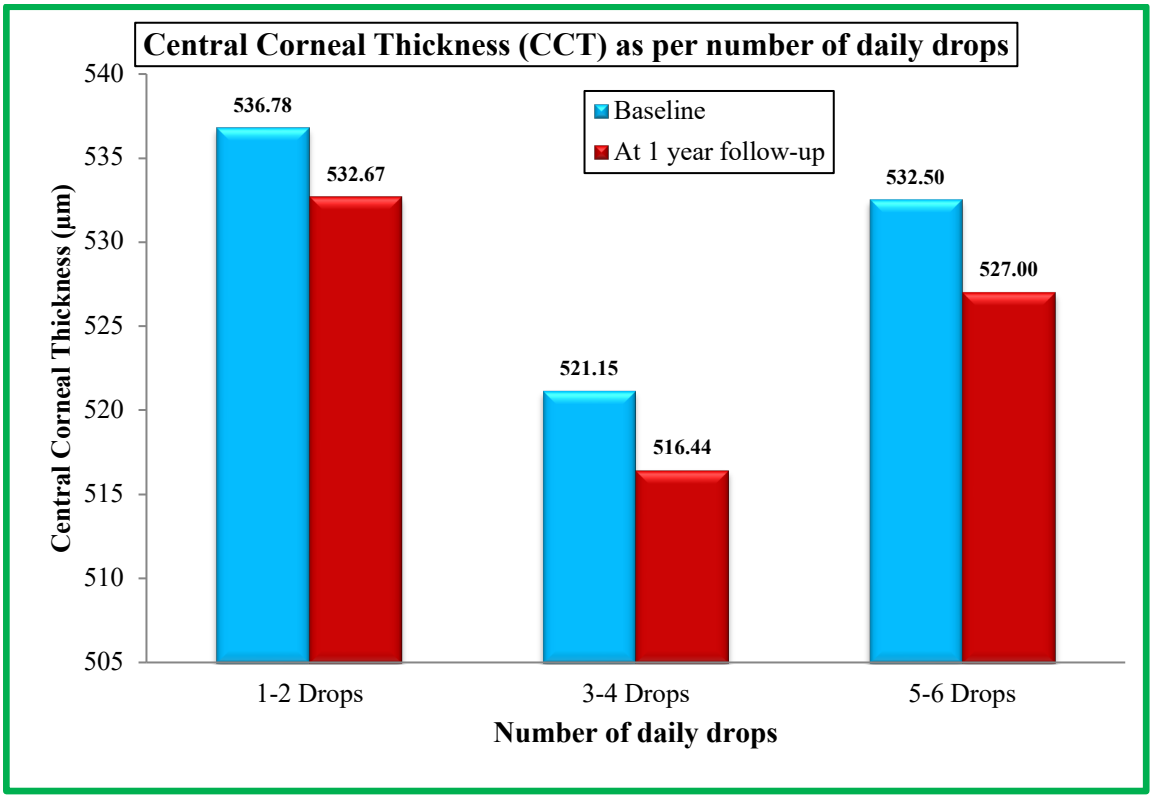


Table 6: Central Corneal Thickness (CCT) as per the number of daily drops at baseline and one-year follow-up

Number of daily drops	Baseline		At 1 year follow-up		Difference	t-value	P-value
	Mean	SD	Mean	SD			
1-2 Drops	536.78	42.18	532.67	42.64	4.11	21.26	<0.001*
3-4 Drops	521.15	37.09	516.44	37.45	4.71	22.40	<0.001*
5-6 Drops	532.50	43.22	527.00	43.35	5.50	15.33	<0.001*

***Statistically significant difference with respect to baseline (P-value<0.05); P-value by paired t-test**



Discussion

This prospective, observational, hospital-based study evaluated 60 patients of Primary Open Angle Glaucoma (POAG) using topical antiglaucoma drugs for a minimum period of 6 months before entering the study. The patients were in the age group of 30-80 yrs with the mean age of 55 ± 11.84 yrs. Our study group consisted of 35 (58.3%) males and 25 (41.7%) females.

Corneal Epithelial Thickness (CET) had a baseline mean value of 60.02 ± 6.04µm which decreased to a mean value of 57.62 ± 6.16µm at 1 year follow up. The difference was 2.40µm with a t-value of 32.26 and a P-value of <0.001 which was statistically significant (Table 1). This was consistent with a study done by Montorio et al [24] which reported a reduction in each CET sector in glaucomatous eyes as compared with the control group. Halkiadakis et al [22] revealed a small but statistically significant reduction of CET in glaucoma patients that uniformly affected all the regions of the cornea.

The comparison between CET values and the number of drugs used by patients showed that patients using 1 drug had a difference of 2.04 µm between the baseline and 1-year follow-up values. The difference was 2.25 µm, 2.68 µm, and 2.86 µm in patients using 2,3 and 4 drugs respectively. The P-value was <0.001 which was statistically significant (Table 2). The comparison between CET values and the number of daily drops used by patients revealed that patients using 1-2 drops had a difference of 2.13 µm between the baseline and 1-year follow-up values. The difference was 2.56 µm and 2.64 µm in patients using 3-4 and 5-6 daily drug drops respectively. The P-value was statistically significant (<0.001) (Table 3). This was in consistence with a study done by Nam et al [23] that determined that age, the total number of medications, and number of daily BAK-containing instillations were associated with a thinner epithelium. Batawi et al [25] used calipers to measure central CET in OCT-derived images of male patients with glaucoma showing reduced, but marginal, difference between glaucoma patients and controls (45.8 vs. 46.9µm, P=0.1). They also reported that the number of topical medications used correlated significantly with CET.

Central Corneal Thickness (CCT) had a baseline value of 529.97 ± 40.8µm which decreased to a mean value of 524.56 ± 41.2µm at 1 year follow up. The difference was 5.42µm with a t-value of 34.29 and a P-value of <0.001 which was statistically significant (Table 4). This was in concordance with a study done by Viswanathan et al [26] which determined that CCT decreased by a mean 12.29 ±13.65 mm (2.26 ±2.52% reduction) in treated eyes over a follow-up period of 6.92 ±1.67 years. Kim and Cho [27] recently showed a statistically significant reduction in CCT by 5.4 µm after 24 months of treatment with latanoprost in patients with NTG. Sen et al [28] reported a percentage reduction rate in CCT of 1.9 ± 2.4% and 2.8 ±1.8% during 24 months of treatment with latanoprost and bimatoprost, respectively.

However, conflicting results have been reported regarding the effects of topical antiglaucoma drugs on CCT. Grueb and Rohrbach [29] found that CCT increased significantly on the 9th day after the use of timolol and it returned to baseline level on the 28th day. Lass et al [30] did not find any significant difference between the baseline CCT and CCT in the first year after the treatment of timolol. Several studies have reported increased CCT in patients using PG analogs. It was thought that the reason for corneal thickening might be the prostaglandin-induced cellular morphological changes in corneal stromal cells. Therefore, more detailed prospective studies with larger sample sizes are needed to investigate this issue.

The comparison between CCT values and the number of drugs used by patients showed that patients using 1 drug had a difference of 5.17 µm between the baseline and 1-year follow-up values. The difference was 5.22 µm, 5.65 µm, and 6.02 µm in patients using 2,3 and 4 drugs respectively. The P-value was <0.001 which was statistically significant (Table 5). The comparison between CCT values and the number of daily drops used by patients revealed that patients using 1-2 drops had a difference of 4.11 µm between the baseline and 1 year follow-up values. The difference was 4.71 µm and 5.50 µm in patients using 3-4 and 5-6 daily drug drops respectively. The P-value was <0.001 which was statistically significant (Table 6). This was in agreement with a study done by Schrems et al [31] which demonstrated that combination therapy with BB + CAI + PG to be associated with the most pronounced reduction of CCT during the follow-up period as compared to patients on monotherapy. This correlated with the number of drugs used and the number of daily BAK-containing instillations.

This study had many limitations. Our study group consisted of a wide variety of patients using topical antiglaucomatous agents, and the number of patients in these groups was relatively unequal. More accurate results can be obtained with a long-term prospective study in a newly diagnosed group of patients using only the same antiglaucomatous medications. Therefore, detailed prospective studies with larger sample sizes and longer follow-up periods are required.

Conclusion:

Glaucoma is a chronic disease for which medical management is the cornerstone

therapy. Prolonged use of topical antiglaucoma drugs has adverse effects on the corneal surface. The values of CET and CCT decreased over the one-year study period. Further, the values were found to be worsened with increasing the number of drugs used and daily drops instilled. Using combination drug products instead of multiple individual drug units reduces the frequency of drug instillation and thereby decreases the burden on the cornea.

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