Original Article

Effects of Glaucoma Treatment on Ocular Surface and Tear Functions: Comparison of Trabeculectomy and Antiglaucoma Drops

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Abstract

Objectives: To investigate tear function and ocular surface disease (OSD) findings in patients with glaucoma who received antiglaucoma medication in one eye and trabeculectomy surgery in the other eye.

Materials and Methods: The patient group included 38 eyes of 19 patients who had undergone trabeculectomy surgery with mitomycin C (MMC) treatment in one eye at least 6 months prior. These eyes were followed up without medication while the fellow eye continued receiving antiglaucomatous medication. The control group comprised 20 eyes of 20 healthy individuals. Demographic data, follow-up period after trabeculectomy, antiglaucoma medications, number of drops per day, and duration of medication were recorded. Tear break-up time (BUT), corneal and conjunctival fluorescein staining, Schirmer II test, and conjunctival impression cytology were performed.

Results: A statistically significant difference was observed in BUT, corneal and conjunctival fluorescein staining, Schirmer II test, and Nelson staging levels in both eyes of patients with glaucoma compared to the control group (p=0.05). Although not statistically significant, BUT, Schirmer II test, punctate staining, and Nelson staging results showed improvement with increasing postoperative time.

Conclusion: In our patient group, antiglaucoma medications and trabeculectomy surgery with MMC induced OSD to a similar degree. No superiority was observed between trabeculectomy with MMC and antiglaucoma drops in terms of OSD incidence.

Keywords: Antiglaucoma drugs, conjunctival impression cytology, glaucoma, ocular surface disease, trabeculectomy

Introduction

The goal of glaucoma treatment is to maintain intraocular pressure within the target range, thereby protecting the optic nerve. Antiglaucoma drugs are usually the first line of treatment. However, prolonged topical antiglaucomatous therapy is associated with an increase in ocular surface disease (OSD). The most important factor in this is the preservatives rather than the active substance.[1]

Trabeculectomy remains the gold standard in glaucoma surgery. The main factor determining the success of trabeculectomy is wound healing. Unlike other surgeries, partial wound healing after surgery is desired. The premature or excessive formation of scar tissue at the interface of the conjunctiva, Tenon's capsule, and episclera at the bleb site results in surgical failure. Antifibrotic agents such as 5-fluorouracil and mitomycin C (MMC) have enhanced the success rates of filtering glaucoma surgery.[2] OSD can occur after trabeculectomy and antimetabolite use.[3]

In this study, glaucoma patients received topical antiglaucoma medication in one eye and MMC-augmented trabeculectomy with no further medical treatment in the fellow eye. The incidence and severity of OSD after treatment were compared between the patients' fellow eyes and with a healthy control group. Hence, we aimed to compare antiglaucoma drugs and MMC-augmented trabeculectomy in terms of OSD occurrence.

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Materials and Methods

Ethical approval was obtained from the Mersin University Faculty of Medicine Clinical Research Ethics Committee (protocol no: 06/251, date: 17.03.2021). The study was conducted according to the principles of the Declaration of Helsinki. Informed consent forms were obtained from all patients and control participants.

Patients who underwent unilateral trabeculectomy with MMC (0.2 mg/mL, 2 minutes) for glaucoma between January 2012 and January 2021 at the Mersin University Medical Faculty Hospital, Department of Ophthalmology were screened. The patient group comprised 38 eyes from 19 patients who underwent trabeculectomy with MMC and subsequent follow-up without medication in one eye while the fellow eye remained unoperated and was treated with various topical antiglaucoma medications.

The control group included the right eyes of 20 healthy volunteers. These individuals sought care at Mersin University Faculty of Medicine Hospital, Department of Ophthalmology between March and May 2021. The control group had no history of OSD or ocular surgery.

The age range was 7 to 80 years in both groups. Exclusions from the study comprised patients who had undergone trabeculectomy less than six months ago, continued to use topical antiglaucoma medication in the operated eye after trabeculectomy, had a history of ocular trauma or surgery other than trabeculectomy, used artificial tears, used contact lenses, were pregnant or lactating, or had a history of uveitis.

All eyes included in the study underwent the tear break-up time (BUT) test, Schirmer II test, corneal and conjunctival fluorescein staining, and conjunctival impression cytology. At least 15 min were allowed between tests. Age and sex of the participant were recorded.

In the patient group, the following details were also recorded: antiglaucoma medications used, number of drops per day, duration of use, and time elapsed since MMC-augmented trabeculectomy (months). All test results were compared between patient subgroups defined according to the time since trabeculectomy (8-47 months vs. ≥48 months).

Tear Break-up Time Test

A standard fluorescein strip was applied to the lower fornix without topical anesthetic. The patient was asked to blink several times to spread the dye well, and the tear film layer was observed under wide illumination using a cobalt blue filter on a slit lamp. The time from the patient's last blink to the first dry area was determined in seconds. This measurement was repeated thrice, and the mean value was recorded as the BUT value. Tear BUT was graded as follows: <5 s (severe), 5-9 s (mild), and ≥10 s (normal).

Schirmer II Test

A 35-mm-long, 5-mm-wide standard filter paper was moistened with topical anesthetic and placed in the outer third of the lower eyelid for the test. Care was taken to prevent the filter paper from touching the cornea. Patients were told to blink if necessary and to keep their eyes open. The wetted portion of filter paper from the lid edge was measured in millimeters after 5 min. The grading used for the test was as follows: <5-mm (severe), 5-10-mm (mild), and ≥11-mm (normal).

Corneal and Conjunctival Fluorescein Staining Test

The corneal staining tests were graded using a slit lamp microscope at x16 magnification, under uniform illumination, and by the same observer. Care was taken to slightly elevate the upper eyelid to evaluate the entire corneal surface. The grading denoted the degree of staining, not the number of stained spots. The Oxford grading scheme was employed to standardize the degree of dye uptake.[4]

Conjunctival Impression Cytology

Samples were obtained from the superotemporal bulbar conjunctiva using one drop of 0.5% proparacaine hydrochloride topical anesthesia (all patients had trabeculectomy surgery in the upper nasal quadrant). Cellulose acetate filter paper with 0.22-µm pore diameter (Millipore) was cut into 5 mm x 5 mm x 5 mm triangles. The filter paper was held with toothless pliers, and the matte surface was pressed against the conjunctiva for 4-5 s. After lifting the edge of the filter paper with pliers, the cell samples were placed face-up in a fixation solution containing glacial acetic acid, 37% formaldehyde, and 70% ethyl alcohol at a volume ratio of 1:1:20. Cellulose acetate filter papers soaked and containing conjunctival epithelial cells were stored in a refrigerator at +4 °C. The samples were fixed to a microscope slide with a metal clip and stained with periodic acid Schiff/hematoxylin/eosin. Cellular changes were staged between 0 and 3 according to the Nelson staging system (Figure 1).[5,6]

Statistical Analysis

Descriptive statistics are presented as mean (± standard deviation) for continuous variables, whereas categorical variables are presented as frequencies and percentages. Independent t-test

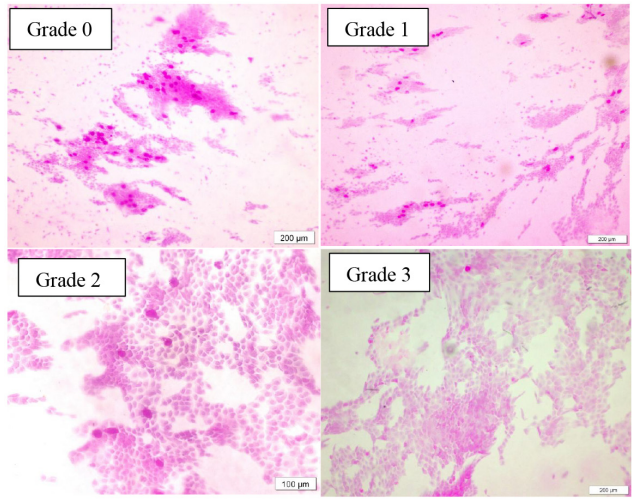

Figure 1. Examples of our conjunctival impression cytology images according to Nelson grading system

was used to determine the difference between the two groups, and one-way analysis of variance was used for more than two groups. The chi-square test was used to analyze categorical variables. The significance level (p value) was set at 0.05 for all variables. All statistical analyses were performed using the Statistica 13 package program.

Results

The study involved 19 glaucoma patients, consisting of 13 males (68.4%) and 6 females (31.6%). Additionally, there were 20 control participants, including 14 males (70%) and 6 females (30%). The mean age of the glaucoma patients was 53.11 (±21.17) years, whereas that of the control group was 56.20 (±19.94) years. There was no statistically significant difference between the patient and control groups in terms of age or sex distribution (p>0.05).

The mean duration of topical antiglaucoma medication was 6.62 (±3.06) years, and the mean number of drops per day was 2.42 (±0.83) drops. The mean follow-up time after trabeculectomy was 38.63±26.29 months.

In the drug group, Schirmer II values were below 5 mm in 1 patient, 5-10-mm in 7 patients, and over 10-mm in 11 patients. In the MMC-augmented trabeculectomy group, Schirmer II values were below 5-mm in 2 patients, 5-10-mm in 5 patients, and over 10-mm in 12 patients. All individuals in the control group had Schirmer II values greater than 10 mm. In the drug group, tear BUT was less than 5 seconds in 4 patients, 5-10 seconds in 4 patients, and longer than 10 seconds in 11 patients. In the MMC-augmented trabeculectomy group, tear BUT was less than 5 seconds in 1 patient, 5-10 seconds in 7 patients, and longer than 10 seconds in 11 patients. BUT was longer than 10 seconds in all individuals in the control group. There were no statistically significant differences between the surgically and medically treated fellow eyes in either test (p>0.05). However, both eyes of the patients had significantly lower results in the BUT and Schirmer II tests when compared with the control group (p<0.05) (Figures 2 and 3).

There was no fluorescein staining in 8 patients in the drug group, while there was mild staining in 4, moderate staining in 5, and severe staining in 2 patients. There was no fluorescein staining in 8 patients in the MMC-augmented trabeculectomy group, while there was mild staining in 3, moderate staining in 7, and severe staining in 1 patient. There was no fluorescein staining in any of the control group individuals. Corneal and conjunctival fluorescein staining did not differ significantly between the surgically and medically treated eyes of patients with glaucoma (p>0.05) but was more severe in patients than controls (p<0.05) (Figure 4).

In conjunctival impression cytology, the distribution of patients staged as grade 0, 1, 2, and 3 was 5, 5, 5, and 4 in the drug group and 2, 7, 3, and 7 in the MMC-augmented trabeculectomy group, respectively (p>0.05). A statistically significant difference was observed between both eyes of the patients and the control group in terms of Nelson staging (p>0.05) (Figure 5).

When patients with postoperative periods of 8-47 months and ≥48 months were compared, there was no statistically significant difference in BUT, Schirmer II, corneal and conjunctival fluorescein staining, or conjunctival impression cytology results (p>0.05, independent t-test). Nevertheless, with an increase in the postoperative period, all test results were observed to improve, although not statistically significantly (Table 1).

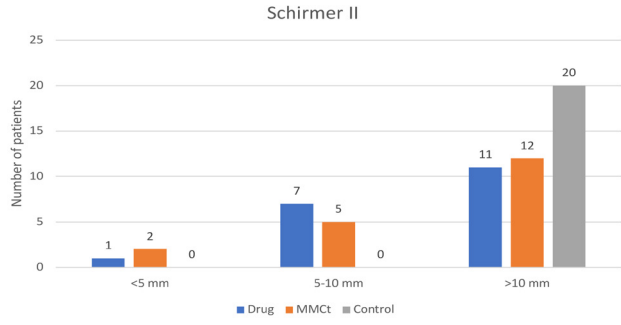

Figure 3. Distribution of Schirmer II results in the drug, MMCt, and control groups
MMCt: Mitomycin C augmented trabeculectomy

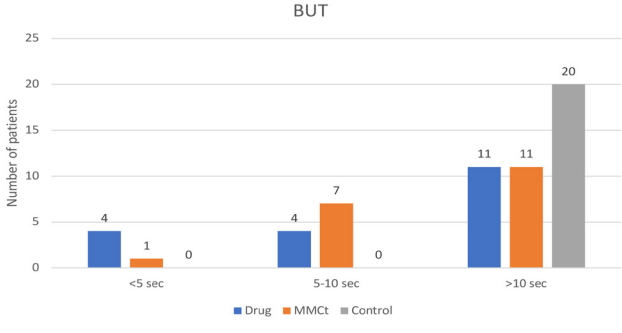

Figure 2. Distribution of tear break-up time results in the drug, MMCt, and control groups
BUT: Tear break-up time, MMCt: Mitomycin C augmented trabeculectomy

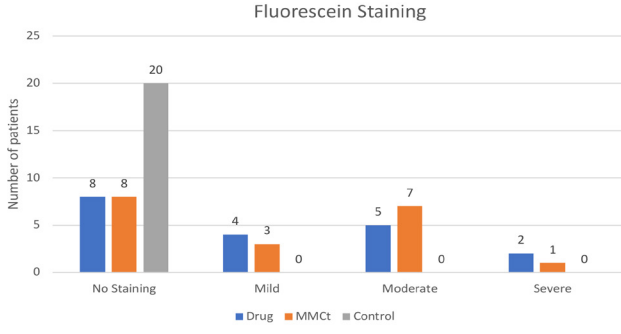

Figure 4. Distribution of fluorescein staining test results (Oxford scheme) in the drug, MMCt, and control groups
MMCt: Mitomycin C augmented trabeculectomy

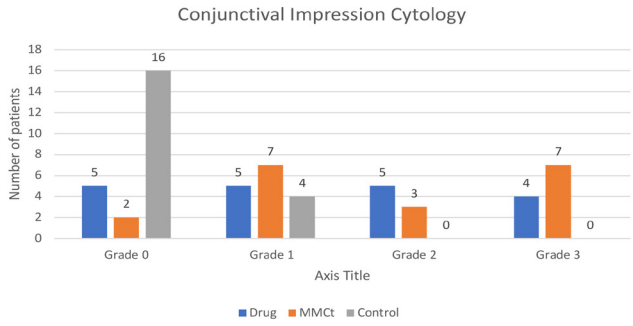

Figure 5. Distribution of conjunctival impression cytology results (Nelson grading system) in the drug, MMCt, and control groups
MMCt: Mitomycin C augmented trabeculectomy

Table 1. Comparison of tear break-up time, Schirmer II, fluorescein staining and conjunctival impression cytology results of 8-47 months and ≥48 months subgroups according to the time since trabeculectomy surgery (independent t-test)

		8-47 months (n=10)	≥48 months (n=9)	p value
BUT	<5 sec	10%	0%	0.553
	5-10 sec	40%	33.3%	
	>10 sec	50%	66.7%	
Schirmer II	<5 mm	20%	0%	0.340
	5-10 mm	20%	33.3%	
	>10 mm	60%	66.7%	
Fluorescein staining	No staining	40%	44.4%	0.699
	Mild	10%	22.2%	
	Moderate	40%	33.3%	
	Severe	10%	0%	
Conjunctival impression cytology	Grade 0	10%	11.1%	0.903
	Grade 1	40%	33.3%	
	Grade 2	10%	22.2%	
	Grade 3	40%	33.3%	

BUT: Tear break-up time

Discussion

In our daily practice, dry eye syndrome is diagnosed based on the results of Schirmer's test, BUT, ocular surface staining with fluorescein, and the presence of ocular irritation symptoms.[7] In glaucoma patients, tear dysfunction is mainly attributed to the chronic administration of preservative-containing glaucoma medications. While moderate dry eye is known to develop with age, the rate of age-related dry eye disease is 15% in patients of comparable age without glaucoma.[8] Given the impact of patient age on the tear film, our study exclusively included patients and controls with similar age and sex distributions.

In a recent study, Yıldırım et al.[9] reported that 45% of ophthalmologists noticed OSD was evident in least 25% of their patients. Antiglaucoma therapy-induced OSD is largely due to preservatives rather than the active molecule.[10,11,12] Benzalkonium chloride (BAK) is the most commonly used preservative. BAK disrupts tear film stability and causes goblet cell loss, conjunctival squamous metaplasia, apoptosis, corneal epithelial barrier disruption, and corneal nerve damage.[13,14,15,16,17,18,19]

Trabeculectomy is a widely used surgical intervention to manage intraocular pressure in patients with glaucoma unresponsive to medical therapy. Previously, MMC was only used as an adjunctive treatment for failed trabeculectomy or complicated cases. Currently, MMC is used for primary trabeculectomy in both adults and children. In our study, all patients with glaucoma underwent trabeculectomy with MMC. Kim[20] indicated potential long-term damage to the bleb's conjunctival epithelium after trabeculectomy with MMC. In subsequent years, through immunofluorescent staining on impression cytology samples taken from the bleb area, Amar et al.[21] demonstrated that blebs without antimetabolites exhibited only scattered inflammatory cells, whereas blebs with MMC showed a higher presence of dendritiform inflammatory cells. Baiocchi et al.[22] found that the inflammatory reaction after trabeculectomy using MMC was more pronounced than that after the surgical procedure associated with the Xen 45 Gel Stent. MMC increases the success rate of trabeculectomy but may have toxic effects on the conjunctiva. Various studies have indicated that trabeculectomy efficiently reduces intraocular pressure and improves control of 24-hour mean pressure but can extensively alter the ocular surface anatomy, inducing a persistent clinical or subclinical inflammatory process.[23,24]

Comparison of tear function tests between the patient and control groups demonstrated significantly lower BUT and Schirmer II values in both eyes of the patients. Schirmer II test results were similar in the trabeculectomy group and topical medication group (p=0.701). Despite the shorter tear BUT in medically treated eyes, there was no statistically significant difference compared to the trabeculectomy group (p=0.270). These results suggest that both antiglaucoma drugs and trabeculectomy with MMC may affect the mucin and aqueous layers of the tear film and result in OSD at a similar rate. The presence of a bleb may also disrupt the uniform distribution of tears on the cornea, leading to worsening of tear function test results. However, there were no data on tear function and degree of ocular surface discomfort in patients before trabeculectomy.

When corneal and conjunctival fluorescein staining results were compared between the patient and control groups, significantly higher Oxford grading scores were observed in both eyes of the patients. Similar results were reported in other studies in which BAK-preserved topical medications were mostly used for treatment. Superficial punctate keratitis has been reported in 50% of patients treated with three drugs per day.[25,26,27,28] This result shows that chronic ocular surface cell damage can occur in

both treatment groups.

Impression cytology is a well-established method to diagnose OSDs. After long-term use of antiglaucoma drugs, ocular surface and tear secretion changes have been noted. There is a relationship between the course of topical antiglaucoma treatment and conjunctival changes like thickened conjunctival epithelium, abnormal keratinization, and loss of conjunctival goblet cells.[29] The most common changes after the use of 0.02% MMC are loss of goblet cells, abnormal nucleus/cytoplasm ratio, less cell-to-cell adhesion, and reduced cellularity.[30] Our comparison of the conjunctival impression cytology samples based on the Nelson staging system revealed a deterioration in the morphological structure of the conjunctival epithelial cells and a significant decrease in goblet cell density in the eyes of glaucoma patients compared to controls. Contrary to our expectation, Nelson staging results were more severe in the trabeculectomy group. However, there was no statistically significant difference in comparison to the topical medication group (p=0.401). This result may be attributed to the fact that patients undergoing trabeculectomy receive multidrug therapy for several years preoperatively, along with the negative effects of MMC and the filtration bleb on the conjunctival epithelium and goblet cells.[10,11,12,22] We also observed an improvement in the conjunctival impression cytology results with an increasing time after trabeculectomy, although the improvement was not statistically significant.

In eyes undergoing trabeculectomy surgery, these outcomes may be attributed to several factors: the chronic impact of BAK on the ocular surface due to long-term topical antiglaucoma treatment received preoperatively; extensive alteration of the ocular surface anatomy by the postoperative bleb; and/or the effect of MMC on the conjunctival epithelium and goblet cells. The number of individuals included in the patient group may also have affected our results. Results may differ in larger patient groups. Studies that follow patients from the initial diagnosis will be useful in detecting ocular surface changes during the treatment process.

In a recent prospective study, Pathak Ray et al.[31] concluded that the ocular surface was affected even in asymptomatic patients in the drug group but near normalcy is possible following trabeculectomy when blebs are diffuse. The authors compared 36 eyes in the trabeculectomy group, 33 eyes in the drug group, and 35 normal eyes. As their study included a larger sample than ours, it could be a valuable study on this subject. In our opinion, our study is important because it is the only study in the literature comparing antiglaucoma drug therapy and trabeculectomy in the same individuals.

Study Limitations

There are limiting factors in this study. The frequency of OSD increases over time in patients with glaucoma. Before trabeculectomy, all patients were receiving maximum topical antiglaucoma therapy. However, no information was available about how long they used this treatment. There was no data regarding the BAK or other preservative content of the drugs used in the patient eyes. However, as one eye of each patient was included in the medication group and the fellow eye was included in the trabeculectomy group, similar medications were used in both groups.

Conclusion

Topical antiglaucoma medications and trabeculectomy surgery with MMC caused similar severity of OSD in our glaucoma patient group. When selecting a medication, it is essential to consider the long-term nature of the treatment. Whenever possible, initiation of the treatment should involve a single drug, and preservative-free alternatives should be considered. After trabeculectomy surgery with MMC, OSD findings tended to improve with a longer follow-up, although the improvement was not statistically significant. Therefore, in terms of OSD in patients with glaucoma, there is no superiority between drug therapy and trabeculectomy with MMC in the early period. However, trabeculectomy with MMC may become more advantageous in later years with the elimination of drug use.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Mersin University Faculty of Medicine Clinical Research Ethics Committee (protocol no: 06/251, date: 17.03.2021).

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: A.Y., Concept: A.Y., A.M., Ö.D., Design: A.Y., A.M., Ö.B., H.S., Data Collection or Processing: A.Y., A.M., P.E., M.B., Ö.B., H.S., Analysis or Interpretation: A.Y., A.M., H.S., Literature Search: A.Y., A.M., Ö.D., P.E., M.B., Writing: A.M., Ö.D., A.Y.

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