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ENDOTHELIAL CELL LOSS FOLLOWING TRABECULECTOMY: A COMPARISON WITH AND WITHOUT MITOMYCIN-C

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Abstract

Introduction: *Adjunctive anti fibrotic agents, such as 5-fluorouracil (5-FU) or mitomycin-C (MMC), are commonly used to increase the success rate of glaucoma filtering surgery. Due to the greater potency and fewer complications, MMC is currently in widespread use in trabeculectomy. MMC is an antibiotic derived from Streptomyces caespitosus with alkylating properties that exerts its most profound cellular toxicity in the late G1 and early S cellular phases.*

Objectives: *To compare the mean corneal endothelial cell loss after trabeculectomy with and without mitomycin-C*

Study design: *Randomized controlled trial*

Settings: *Department of Ophthalmology, Allied Hospital, Faisalabad*

Study duration: *18th January 2024 to 17th July 2024*

Materials & Methods: *A total of 60 patients with primary open angle glaucoma, of age 30-70 years of either gender were included. Patients with ocular trauma, any intraocular surgery, previous history of trabeculectomy, endothelial disorders such as corneal guttae, Fuchs endothelial dystrophy, neovascular glaucoma were excluded. Group A patients were undergone trabeculectomy with adjunctive mitomycin-C while group B patients were undergone trabeculectomy alone. Post-trabeculectomy endothelial cell counts was recorded with the help of specular microscope.*

Results: *In my study, mean endothelial cell density pre-operatively in Group A (trabeculectomy with mitomycin-C) was 2349.80 ± 93.14 while in Group B (trabeculectomy without mitomycin-C) was 2364.93 ± 109.78. Mean endothelial cell density post-operatively in Group A (trabeculectomy with mitomycin-C) was 2179.80 ± 79.85 while in Group B (trabeculectomy without mitomycin-C) was 2282.83 ± 109.51. Mean change in endothelial cell density in Group A (trabeculectomy with mitomycin-C) was 170.0 ± 9.99 while in Group B (trabeculectomy without mitomycin-C) was 82.43 ± 7.38.*

Conclusion: *This study concluded that mean corneal endothelial cell loss after trabeculectomy with mitomycin-C is significantly higher than without mitomycin-c*

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INTRODUCTION

The definition of glaucoma has changed drastically since its introduction around the time of Hippocrates (approximately 400 BC). The word glaucoma came from the ancient Greek word glaucosis, meaning clouded or blue-green hue, most likely describing a patient having corneal edema or rapid evolution of a cataract precipitated by chronic elevated pressure. Over the years, extensive refinement of the concept of glaucoma has continued, accelerating, especially in the last 100 years, to the present date.[1,2]

Glaucoma is currently defined as a disturbance of the structural or functional integrity of the optic nerve that causes characteristic atrophic changes in the optic nerve, which may also lead to specific visual field defects over time. This disturbance usually can be arrested or diminished by adequate lowering of intraocular pressure (IOP). Nevertheless, some controversy still exists as to whether IOP should be included in the definition, as some subsets of patients can exhibit the characteristic optic nerve damage and visual field defects while having an IOP within the normal range. The generic term glaucoma should only be used in reference to the entire group of glaucomatous disorders as a whole, because multiple subsets of glaucomatous disease exist. A more precise term should be used to describe the glaucoma, if the specific diagnosis is known.[2]

Glaucoma can be roughly divided into two main categories, "open-angle" and "closed-angle" (or "angle closure") glaucoma. The angle refers to the area between the iris and cornea, through which fluid must flow to escape via the trabecular meshwork. Closed-angle glaucoma can appear suddenly and is often painful; visual loss can progress quickly, but the discomfort often leads patients to seek medical attention before permanent damage occurs. Open-angle, chronic glaucoma tends to progress at a slower rate and patients may not notice they have lost vision until the disease has progressed significantly.[3,4]

The aim of glaucoma treatments is to slow disease progression while preserving visual functions without changing the patient's quality of life. In general, these treatments are primarily designed to lower the intraocular pressure (IOP), with first approach utilizing medical therapies with anti-glaucoma drugs.[5] When maximal tolerable medical therapy is not able to sufficiently lower the IOP, patients are treated using trabeculectomy in order to prevent optic nerve damage or visual field deterioration.[6] Trabeculectomy is the most commonly used glaucoma surgical procedure for lowering intra ocular pressure by providing an alternate drainage pathway from the anterior chamber to the sub conjunctival space. However, the success rate of this surgery has been limited by postoperative fibroblast proliferation and scarring of the filtering bleb.[7]

Adjunctive anti fibrotic agents, such as 5-fluorouracil (5-FU) or mitomycin-C (MMC), are commonly used to increase the success rate of glaucoma filtering surgery. Due to the greater potency and fewer complications, MMC is currently in widespread use in trabeculectomy.[8] MMC is an antibiotic derived from Streptomyces caespitosus with alkylating properties that exerts its most profound cellular toxicity in the late G1 and early S cellular phases.[9] It is suggested that in high doses, MMC has a cytotoxic effect that is independent of cell cycle. Moreover, it is described as a radiomimetic agent with possible long-term consequences on tissues.[6] In trabeculectomy, MMC may penetrate into adjacent ocular tissues, beyond its application site. Since corneal endothelial cells lack division capacity, possible insults are irreparable and cell density diminishes gradually.[10] In a study, mean corneal endothelial cell loss was 157.69 ± 109.29 when trabeculectomy was done with the use of adjunctive mitomycin-C while mean endothelial cell loss was 71.93 ± 140.22 when the trabeculectomy was done without the use of adjunctive mitomycin-C.[11] In another study, mean endothelial cell loss was 283 ± 66.50 when trabeculectomy was done with the use of adjunctive mitomycin-C while mean endothelial cell loss was 72.50 ± 19.25 when the trabeculectomy was done without the use of adjunctive mitomycin-C.[7]

In majority of our setups, mitomycin-C is commonly applied during trabeculectomy in order to prevent fibrosis. The aim of the present study is to explore either mitomycin-C is associated with minimum changes in endothelial cell density or not. This study aims to restrict the over-zealous use of mitomycin-C in trabeculectomy procedure by ophthalmologists, thus preventing endothelial cell loss.

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Methods & Materials:

This randomized controlled trial was conducted at the Department of Ophthalmology, Allied Hospital, Faisalabad. The study spanned a duration from 18th January 2023 to 17th July 2023. A total of 60 patients were enrolled in the study, with 30 patients allocated to each group. The sample size was determined using OpenEpi online software, based on a mean endothelial cell loss of 157.69 ± 109.298 for trabeculectomy with mitomycin-C and 71.93 ± 140.228 for trabeculectomy without mitomycin-C, assuming a power of 80% and a significance level of 5%.

A non-probability, consecutive sampling technique was used to select the study participants. Inclusion criteria included all patients diagnosed with primary open-angle glaucoma, aged between 30 and 70 years, regardless of gender. Patients were excluded if they had a history of ocular trauma, previous intraocular surgery, prior trabeculectomy, or any endothelial disorders such as corneal guttae, Fuchs endothelial dystrophy, or neovascular glaucoma.

After receiving ethical approval, 60 eligible patients were selected and informed consent was obtained from each participant after explaining the study's nature and risk/benefit ratio. Patients were then randomly assigned into two groups (A and B), each consisting of 30 patients, using the lottery method. Preoperative endothelial cell counts were recorded using a specular microscope. Group A underwent trabeculectomy with adjunctive mitomycin-C, while Group B underwent trabeculectomy without mitomycin-C. The surgical procedure involved performing a superior limbal peritomy and creating a scleral flap and window in each patient. In Group A, mitomycin-C was applied on the scleral flap. Postoperative endothelial cell counts were also recorded using a specular microscope.

For statistical analysis, data were entered and analyzed using SPSS version 25.0. Mean and standard deviation were calculated for continuous variables including age, disease duration, preoperative and postoperative corneal endothelial cell counts, and endothelial cell loss. Gender distribution was reported in terms of frequency and percentage. The comparison of mean endothelial cell loss between the two groups was made using an independent t-test, with a p-value of ≤0.05 considered statistically significant. Furthermore, potential effect modifiers such as age, gender, and duration of disease were stratified, and the independent t-test was again applied to evaluate their impact on endothelial cell loss, with a p-value of ≤0.05 taken as significant.

Results:

Age range in this study was from 30 to 70 years with mean age of 50.11 ± 6.31 years. The mean age of patients in group A was 50.07 ± 6.37 years and in group B was 50.30 ± 6.39 years. Majority of the patients 33 (55.0%) were between 51 to 70 years of age as shown in Table 1.

Table 1: Age distribution for both groups (n=60).

Age (years)	Group A (n=30)		Group B (n=30)		Total (n=60)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
30-50	14	46.67	13	43.33	27	45.0
51-70	16	53.33	17	56.67	33	55.0
Mean ± SD	50.07 ± 6.37		50.30 ± 6.39		50.11 ± 6.31	

Out of 60 patients 29 (48.33%) were males and 31 (51.67%) were females with male to female ratio of 1:1.1 as shown in Table II. Mean duration of disease was 9.85 ± 1.98 months (Table 2).

Table 2: Distribution of patients according to duration (n=60).

Duration (months)	Group A (n=30)		Group B (n=30)		Total (n=60)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
≤12	27	90.0	26	86.67	53	88.33
>12	03	10.0	04	13.33	07	11.67

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Mean ± SD	**9.83 ± 1.98**	**9.97 ± 1.96**	**9.85 ± 1.98**

Mean endothelial cell density pre-operatively in Group A (trabeculectomy with mitomycin-C) was 2349.80 ± 93.14 while in Group B (trabeculectomy without mitomycin-C) was 2364.93 ± 109.78. Mean endothelial cell density post-operatively in Group A (trabeculectomy with mitomycin-C) was 2179.80 ± 79.85 while in Group B (trabeculectomy without mitomycin-C) was 2282.83 ± 109.51. Mean change in endothelial cell density in Group A (trabeculectomy with mitomycin-C) was 170.0 ± 9.99 while in Group B (trabeculectomy without mitomycin-C) was 82.43 ± 7.38 as shown in Table 3 (P-value = 0.0001).

Table 3: Comparison of the mean corneal endothelial cell loss after trabeculectomy with and without mitomycin-C.

Endothelial cell density (ECD)	**Group A (n=30)** **Mean ± SD**	**Group B (n=30)** **Mean ± SD**	**P-value**
Pre-operative	2349.80 ± 93.14	2364.93 ± 109.78	**0.567**
Post-operative	2179.80 ± 79.85	2282.83 ± 109.51	**0.0004**
Change in ECD	170.0 ± 9.99	82.43 ± 7.38	**0.0001**

Stratification of mean change in endothelial cell density with respect to age groups is shown in Table 4 which showed significant difference in mean change in endothelial cell density in all age groups among both groups.

Table 4: Stratification of mean Change in ECD with respect to age groups.

Age of patients (years)	**Group A (n=30)** **Change in ECD**		**Group B (n=30)** **Change in ECD**		**P-value**
	Mean	SD	Mean	SD	
30-50	170.29	10.68	81.77	6.27	**0.0001**
51-70	169.75	9.69	82.94	8.29	**0.0001**

Similarly statistically significant difference was found in mean change in endothelial cell density in both genders among both groups as shown in Table 5.

Table 5: Stratification of mean Change in ECD with respect to gender.

Gender	**Group A (n=30)** **Change in ECD**		**Group B (n=30)** **Change in ECD**		**P-value**
	Mean	SD	Mean	SD	
Male	166.62	9.76	84.81	6.26	**0.0001**
Female	172.59	9.64	79.71	7.84	**0.0001**

Stratification of mean change in endothelial cell density with respect to duration of disease is shown in Table 6.

Table 6: Stratification of mean Change in ECD with respect to duration.

Duration (months)	**Group A (n=50)** **Change in ECD**	**Group B (n=50)** **Change in ECD**	**P-value**

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	Mean	SD	Mean	SD	
≤12	170.44	10.44	82.54	7.39	0.0001
>12	166.0	1.73	81.75	8.46	0.0001

Discussions:

Mitomycin-C (MMC) was first isolated from cultures of Streptomyces caespitosus by Hata in 1956.[12] Since then, it has been widely used intraoperatively for pterygium excision, trabeculectomy, and surface ablation keratorefractive procedures. Additionally, it is used topically in a cyclic fashion for primary or recurrent ocular surface squamous neoplasia.[13] Having been found safe and effective in animals, MMC was suggested for application during surface ablation procedures to reduce postoperative haze formation.[14,15] It can effectively reduce haze formation and hence, improve the predictability of visual outcomes following refractive surgery. Despite these advantages, MMC can potentially damage all three main corneal cell types including epithelial (differentiated epithelium and limbal cells), stromal (keratocytes), and endothelial cells. Several studies have investigated the effect of a single intraoperative dose of MMC during refractive surgery on the corneal endothelium.

Some clinical[16,17] and laboratory[18,19] studies have reported significant corneal endothelial toxicity. However, the majority of clinical studies have reported no significant change in corneal endothelial density or morphology with follow-up period ranging from 3 to 18 months.[20,21] Most studies on MMC have employed a short duration of exposure, less than 20 seconds. Since different durations of MMC application have been used, discrepancies in the findings of these studies make it difficult to reach a definite conclusion regarding the safety of MMC for corneal endothelial cells.

I have conducted this study to compare the mean corneal endothelial cell loss after trabeculectomy with and without mitomycin-C. In my study, mean endothelial cell density pre-operatively in Group A (trabeculectomy with mitomycin-C) was 2349.80 ± 93.14 while in Group B (trabeculectomy without mitomycin-C) was 2364.93 ± 109.78. Mean endothelial cell density post-operatively in Group A (trabeculectomy with mitomycin-C) was 2179.80 ± 79.85 while in Group B (trabeculectomy without mitomycin-C) was 2282.83 ± 109.51. Mean change in endothelial cell density in Group A (trabeculectomy with mitomycin-C) was 170.0 ± 9.99 while in Group B (trabeculectomy without mitomycin-C) was 82.43 ± 7.38. In a study, mean endothelial cell loss was 283 ± 66.50 when trabeculectomy was done with the use of adjunctive mitomycin-C while mean endothelial cell loss was 72.50 ± 19.25 when the trabeculectomy was done without the use of adjunctive mitomycin-C.[7]

A study conducted by Maria et al. showed a mean endothelial cell loss of 172 after trabeculectomy without mitomycin C.[6] A study done by Paulsen at Frederiksberg University showed a mean endothelial cell loss of 293 ±643 after mitomycin C augmented trabeculectomy.[22] A study done by Sihota in 1998 showed an endothelial cell loss of 70 with trabeculectomy alone as compared to 265 when done with mitomycin.[8] Dios et al. studied and found that corneal endothelial cell loss pf 464 cells after trabeculectomy with mitomycin C in their study. These results are almost similer to the results shown in the study done by researcher.[23]

In a local study, preoperatively, the mean endothelial cell count in group undergoing trabeculectomy with mitomycin C was 2284.10 ±49.43 while it was 2250.93 ±56.25 in the other group showing a significant difference (p=0.018) between both the groups. Postoperatively, the mean endothelial cell count in group undergoing trabeculectomy with mitomycin C was 2008.8 while it was 2105.0 in the other group showing a significant difference at p<0.0001.[11]

Experiments have confirmed direct toxicity of MMC to endothelial cells,[24] but some authors believe that with the concentrations and methods used in trabeculectomy, MMC is unlikely to cause endothelial damage.[25,26] Pastor and associates described a 11% endothelial cell loss in humans, three months after MMC-supplemented trabeculectomy.[27] A prospective controlled clinical study has demonstrated endothelial cell loss 3 and 12 months after MMC-augmented trabeculectomy.[8] Others have found that 5-FU, and MMC cause similar changes in the corneal endothelium.[28]

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However, some clinical studies found that there was no significant MMC related endothelial toxicity, following combined glaucoma and cataract surgery, or trabeculectomy alone.[29]

Another prospective controlled study did not find a significantly higher cell loss in MMC group, as compared to the control group.[30] Zarei et al[7] observed that cell loss of 3.4% in the control group without the use of MMC in the first month and loss of 7.2% in the MMC group. However, the endothelium was of the central cornea and did not assess the peripheral cornea. So, significant regional changes in cell density could not be understood. Endothelial cell toxicity may be localized or more prominent at the site of application, and central corneal endothelial assessment may not actually reflect the whole cornea.

These discrepancies observed in clinical studies may be attributable to variations in study design, sample size, surgical technique and follow-up period. Such discrepancies may also reflect that the effect of MMC on CECD is small. While this small cell loss would probably cause no significant clinical problem, a low or borderline preoperative endothelial cell count could significantly be affected by the intraoperative use of MMC, leading to a clinically decompensated cornea, as reported by some authors.[31]

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