

The Results of Trabeculectomy with Antimetabolites in Elderly Patients: A Retrospective Study

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ABSTRACT

Objective: To examine the effectiveness and results of primary trabeculectomy with 5-fluorouracil (group 1) or mitomycin-C (group 2) in elderly patients.

Materials and Methods: This was a retrospective study including 67 eyes with primary open-angle glaucoma that underwent primary trabeculectomy with group 1 or group 2. Patients who were followed up for less than 1 year or were under 55 years of age were excluded from the study. Surgical success was evaluated according to a decrease in cup/disk ratio and reduction of intraocular pressure without any topical medication.

Results: The mean ages of participants were 65.7 years (range 59–88) and 65.9 years (range 59–74) in groups 1 and 2, respectively. The mean preoperative and postoperative intraocular pressure values were 31.3 ± 5.7 mmHg (range 17–46) and 14.8 ± 0.4 mmHg (range 10–21) in group 1 ($p < 0.001$) and 31.5 ± 7.4 mmHg (range 18–52) and 14.8 ± 2.9 mmHg (range 10–21) in group 2 ($p < 0.001$).

Conclusion: The use of 5-fluorouracil or mitomycin-C during primary trabeculectomy is associated with high postoperative success rates. There were no significant differences between 5-fluorouracil and mitomycin-C in terms of intraocular pressure reduction.

Keywords: Trabeculectomy, 5-fluorouracil, mitomycin-C, intraocular pressure

INTRODUCTION

Glaucoma is a chronic, progressive optic neuropathy characterized by a progressive loss of ganglion cells, and it leads to a characteristic visual function loss [1]. The increasing prevalence of glaucoma with aging is expected to continue to reduce patients' quality of life [1]. In addition, glaucoma has a significant effect on the economy [1]. Older patients with glaucoma have difficulty in social activities [2]. Moreover, the elderly are more likely to have systemic diseases, which may affect their

visual capacities and place them at a greater risk for having surgery [2]. Prior research has consistently found that patients with chronic eye diseases have high rates of emotional problems; Popescu ML et al. showed the relationship between eye disease and depression, where visually limiting eye disease is associated with depression in older adults [3]. Intraocular pressure (IOP) is considered to be a major risk factor for glaucoma [1]. Trabeculectomy, which was initially described by Cairns in 1968

and modified by Watson in 1970, is considered the "gold standard" for filtration surgery [4,5]. However, fibrosis of the filtration site is one of the main reasons for primary failure of glaucoma filtering surgery [6]; fibrosis most commonly occurs at the level of the episclera, leading to flap fibrosis and eventually bleb failure [6].

In the early 1980s, 5-fluorouracil (5-FU) and mitomycin-C (MMC) were found to be effective antimetabolites in inhibiting fibroblastic activity and increasing the success rates of trabeculectomy [7-9]. 5-FU was the first antimetabolite drug used to inhibit fibroblast proliferation and prevent scarring via antagonizing pyrimidine metabolism and inhibition of DNA synthesis. The Fluorouracil Filtering Surgery Study (FFSS) demonstrated that corneal epithelial toxicity and transient visual acuity (VA) loss were common side effects of 5-FU [7,10,11]. This study recommended 5-FU after filtering surgery in eyes with uncontrolled glaucoma following cataract extraction and in phakic eyes after failed filtering surgery [10,11]. MMC is an antibiotic agent with antiproliferative properties, and it is derived from the fungus *Streptomyces caespitosus* [12]. MMC is effective in increasing the success of trabeculectomy through its inhibition of the proliferative phase of the wound-healing pathway, and it is much more potent than 5-FU [13,12]. The aim of this study was to describe the follow-up results of the use of intraoperative 5-FU or MMC in elderly patients who underwent primary trabeculectomy.

MATERIALS and METHODS

The medical records of patients with a diagnosis of progressive glaucoma with uncontrolled IOP despite using a maximum dose of anti-glaucomatous agents were evaluated retrospectively. These patients underwent primary trabeculectomy intraoperatively using 5-FU or MMC between January 1, 2009, and December 30, 2019, in the department of glaucoma at our university's school of medicine. This study was approved by the university ethics committee. Informed consent was obtained from all patients before the surgical procedure was performed. Standard data were collected from the patients' documents and used to record demographic characteristics, pre- and postoperative IOP, VA,

and optic disk cup/disk (C/D) ratios. The exclusion criteria were as follows: patients under 55 years of age, follow-up of less than 1 year, diagnosis of secondary glaucoma, other ocular surface disorders (dry eye etc) and a history of previous laser trabeculectomy or other ocular surgeries. The main inclusion criterion was uncontrolled IOP despite maximum tolerable medications. Sixty-seven eyes of 67 patients with primary open-angle glaucoma were enrolled in the study. Forty-three eyes received intraoperative 5-FU (group 1) and 24 received MMC (group 2) intraoperatively. Complete ophthalmologic examinations were performed for both study groups before and 12 months after the surgical procedure. Patients with under 1 year of follow-up after the surgery were excluded. The examinations consisted of VA with the logarithm of the minimum angle of resolution (logMAR), slit-lamp biomicroscopy, assessing IOP with an Goldman applanation tonometer, and direct or indirect ophthalmoscopy to determine the C/D ratio. Efficacy criterias for trabeculectomy were targeted IOP and the ability to be maintained at a certain level.

Surgical Technique

A limbal-based conjunctival flap was prepared [6,14,15]. To accomplish this, a rectangular limbal-based superficial scleral flap incision (5 x 4 mm) was dissected until the surgical limbus was seen [6,14,15]. The conjunctival and superficial scleral flaps were then dissected. 5-FU (50 mg/ml for 5 minutes) or MMC (0.2 mg/ml for 2 minutes) was soaked in a sponge and placed over the scleral dissection area [6,14,15]. After the sponge was removed, the area was irrigated with normal saline. The trabeculectomy was then completed with a rectangular deep corneo-scleral block excision via Kelly's punch [6,14,15]. A peripheral iridectomy was performed. The superficial scleral flap was secured with 10/0 silk suture, and the conjunctiva was sutured with 8/0 Vicryl. A subconjunctival antibiotic was injected into the inferior fornix. Postoperative antibiotics (fourth-generation fluoroquinolone, 4 x 1 for 7 days) and steroid drops (prednisolone acetate 1% for several weeks) were used tapered from eight times over a period of 12 weeks.

Statistical Analysis

Patient data were entered into a database and analyzed using SPSS 21.0 for Windows (SPSS Inc.,

Chicago, IL). Continuous variables, including age and IOP, were not normally distributed according to the Shapiro–Wilks test, and thus, they were subsequently assessed using the Mann–Whitney–Wilcoxon test, which does not assume parametric distribution. Categorical data, including sex and visual acuity, were analyzed using the Fisher exact or Pearson correlation test.

RESULTS

Sixty-seven eyes of 67 patients who fulfilled the eligibility criteria were included in the study. There were 43 eyes in the 5-FU group (group 1) and 24 eyes in the MMC group (group 2). Preoperative characteristics of patients are given in Table 1. There was no significant difference between the mean age ($p = 0.329$) and gender ($p = 0.423$). The mean follow-up time was 14 months (12–18 months). The mean preoperative IOP among group 1 of patients was 31.3 ± 5.7 (range 17–46) mmHg, and the postoperative IOP was 14.8 ± 2.6 (range 10–21), showing a significant decrease ($p < 0.001$). There was a significant difference between using MMC and decreasing the postoperative IOP ($p < 0.001$; Table 2). We could not demonstrate any difference in effectiveness between 5-FU and MMC in decreasing IOP, VA, and C/D ($p = 0.529$, $p = 0.690$, $p = 0.849$).

DISCUSSION

In this study, both antimetabolite agents were effective in decreasing IOP. Statistical analysis also showed a significant difference between the preoperative and postoperative IOP, VA, and C/D findings in elderly patients. We could not demonstrate any difference in effectiveness between 5-FU and MMC in decreasing IOP. Although the number of participants was different between the two groups, the mean preoperative IOPs were similar.

Glaucoma is an important problem for elderly patients' social lives [2,16]. Reading, walking, and eating can sometimes be difficult for glaucoma patients [2,16]. Visual field (VF) defects are particularly important for progressive disease. Therefore, early treatment could be effective for glaucoma [17].

Ohnel H et al. analyzed the Early Manifest Glaucoma Trial (EMGT) and demonstrated that, in eyes with manifest glaucoma, progression in the VF was detected first more than four times as often as progression in the optic disk [18]. Leske MC et al. assessed factors for progression in EMGT, including the effect of EMGT treatment [19]; these researchers showed that the effect of initial IOP reduction was a major factor for outcome and progression was increased with higher baseline IOP, so IOP reduction is especially important with trabeculectomy [20].

Table 1. Demographics of patients treated with trabeculectomy.

	5-fluorouracil Group 1 (n=43)	Mitomycin C Group 2 (n=24)	p
Age (years) [mean \pm SD] (range)	65.7 \pm 18.6 (59-82)	65.9 \pm 18.6 (59-74)	0.329
Gender (Male/Female)	23/20	13/11	0.423

Table 2. Comparison of preoperative and postoperative parameters patients with 5-Fluorouracil and Mitomycin C group.

Parameters	5-fluorouracil Group 1 (n=43) mean \pm SD (range)		p	Mitomycin C Group 2 (n=24) mean \pm SD (range)		p
	Preoperative	Postoperative		Preoperative	Postoperative	
IOP (mmHg)	31.3 \pm 5.7 (17-46)	14.8 \pm 2.6 (10-21)	<0.001*	34.2 \pm 7.4 (18-52)	14.8 \pm 2.9 (10-21)	<0.001*
Visual acuity (logMAR)	0.7 \pm 0.2 (0.3-1.0)	0.6 \pm 0.3 (0.3-1.0)	<0.001*	0.6 \pm 0.3 (0.5-1.0)	0.5 \pm 0.3 (0.2-1.0)	0.001*
Cup/Disc ratio	0.8 \pm 0.1 (0.7-0.9)	0.7 \pm 0.1 (0.5-0.9)	<0.001*	0.8 \pm 0.1 (0.6-0.9)	0.8 \pm 0.9 (0.6-0.9)	0.005*

IOP: Intraocular pressure, logMAR: Logarithm of the minimum angle of resolution, * denotes statistical significance.

The ideal measurement of success in trabeculectomy is to prevent further changes in the glaucomatous optic nerve head and loss of VA. In this study, we evaluated these parameters and found significant differences. Here, after trabeculectomy with antimetabolites, IOP, which is the major risk factor for progression, was significantly reduced. Previously, Montolino FGJ et al. determined the benefit of glaucoma surgery [21]. In this study, glaucoma surgery was not found to be significantly associated with visual performance [21]. Duman F et al. compared the surgical outcomes of trabeculectomy performed in patients above 80 years with those of younger controls [2]. After 1 year, the failure rate was 31.3% in the elderly group, which is not significantly different from that of younger patients ($p = 0.98$) [2]. However, these studies did not collect sufficient information about elderly patients.

In their study on 108 patients, Singh et al. concluded that 5-FU and MMC had equal efficiency and safety in primary trabeculectomy in our study. In addition, both antimetabolites have been found to be efficient in decreasing postoperative IOP; however, in Singh et al.'s study, they found that these agents had no statistically significant role in improving VA or C/D [22]. In the present study, the findings were similar, but VA was improved after 1 year of follow-up. 5-FU and MMC had similar efficiency and safety between their study and the present one.

Stone RT et al. reported an increase in the success rate of surgery among patients who received MMC (0.3 mg/ml); the present study manifested an 84% success rate during 11.9 months of follow-up [23]. According to our statistics, MMC is as effective as 5-FU in lowering IOP, although we did not administer different dosages of antimetabolite agents. In this study, we excluded patients with other intraocular surgeries, such as combined phacoemulsification or previous laser trabeculoplasty. However, Carlson et al. reported that using intraoperative MMC can be effective in lowering IOP in cases that undergo trabeculectomy combined with phacoemulsification [24]. They followed 29 patients for about 6–30 months using a double masked method [24]. The effectiveness of MMC compared with placebo was significantly high. This result was also determined by other studies that suggested the use of MMC was beneficial in combined surgeries [9,22]. Goldenfeld et al. demonstrated that

adjunctive preoperative 5-FU reduces the need to use antiglaucomatous drops after filtration surgery and can effectively control postoperative IOP [25]. In our study, we did not compare preoperative and postoperative numbers of medications patients used, and this was one of the study's limitations. Wilkins et al. reviewed 11 trials, which were divided into three groups. They reported successful results of intraoperative MMC and significant reduction of IOP. They mentioned no obvious changes in preoperative and postoperative VA [12].

Cankaya AB et al. demonstrated that repeat trabeculectomy with MMC has high success rates in patients with previously failed trabeculectomy despite the need for a higher number of antiglaucoma medications [25]. Antifibrotic agents should always be considered with trabeculectomy for glaucoma.

Our results should be interpreted in light of their potential limitations. The major limitation of the current study is its retrospective design; prospective collection of data can naturally provide for more standardized acquisition of study outcome measures. The study sample size was relatively limited. However, our results showed that adjunctive 5-FU and MMC improved the outcome success rate of trabeculectomy. To establish the effectiveness of postoperative antifibrotic agents, at least the following clinical factors must be identical in the groups to be compared: types of disease, age and race of the patients, surgical procedures, indications for surgery, and postoperative care. Another limitation is that the number of patients in each group was not equal, although we considered age, sex, risk factors, and type of glaucoma in dividing the groups. We did not include postoperative complications in our study. We did not have sufficient visual field findings so this is the important limitation for analyse the patients' results.

In conclusion, the results of the current study suggest that antifibrotic agents could decrease the IOP of elderly patients' glaucomatous eyes. As such, these agents may be an appropriate non-surgical alternative in patients with advanced glaucoma who do not wish to undergo re-trabeculectomy, or they may be utilized on a temporary basis to delay the need for such invasive procedures. Further prospective studies, with larger population sizes

and longer follow-up periods, are recommended to assess the long-term functional and structural effects of the antifibrotic agents on eyes with glaucoma in elderly patients.

CONFLICT of INTEREST STATEMENT

The authors declare that there is no conflict of interest.

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