

# Augmenting trabeculectomy in glaucoma with subconjunctival mitomycin C versus subconjunctival 5-fluorouracil: a randomized clinical trial

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**Objective:** The aim of this study was to compare the efficacy of augmenting trabeculectomy with subconjunctival mitomycin C (TMMC) versus 5-fluorouracil (T5-FU) in lowering intraocular pressure (IOP).

**Methods:** Forty eyes from 40 patients referred to the Nikoukari Ophthalmology University Hospital, Tabriz University of Medical Sciences, Tabriz, Iran, were enrolled in a randomized clinical trial. Patients with high-risk open angle glaucoma were allocated to receive either subconjunctival TMMC or T5-FU.

**Results:** Mean overall preoperative IOP was 30.8 mmHg. Mean preoperative IOPs in the TMMC and T5-FU groups were  $31.2 \pm 9.8$  and  $30.6 \pm 9.9$  mmHg, respectively. Postoperatively, mean IOPs were  $11.43 \pm 4.9$  and  $13.6 \pm 3.9$  mmHg, respectively for TMMC and T5-FU groups after 6 months. In spite of some existing descriptive differences in IOP between the groups, statistical tests showed no difference in mean and median IOP. Three cases of hypotonia (IOP < 6 mmHg) and 1 case of epithelial keratitis were detected.

**Conclusion:** TMMC and T5-FU appeared to have similar efficacy in lowering IOP.

**Keywords:** glaucoma, trabeculectomy, mitomycin C, 5-fluorouracil

## Introduction

Trabeculectomy aims to decrease intraocular pressure (IOP) by allowing the passage of aqueous humor from the anterior chamber to the subconjunctival space. The main reason for failure of filtering surgery is fibroblast proliferation and subsequent scar formation at the surgical site. Recent ongoing research has found some remedies to prevent this, and improve surgical success by inhibiting scar formation. Antimetabolites, including mitomycin C (MMC) and 5-fluorouracil (5-FU), were first used to modify the wound-healing response in the early 1980s. Although an optimum therapy with good efficacy and low complication rate is not yet available, MMC and 5-FU are currently used for this purpose. MMC is an antimetabolite used during the initial stages of a trabeculectomy to prevent excessive postoperative scarring and thus reduce the risk of failure.<sup>1</sup> Similarly 5-FU can be used for the same purpose.<sup>2</sup> MMC and 5-FU are typically used in eyes at high risk for bleb failure, and are used by researchers and clinicians as adjuncts to trabeculectomy surgery (herein, TMMC and T5-FU), but using different protocols and dosages. Most of the evidence on efficacy of TMMC and T5-FU is based on studies conducted separately for these two protocols rather than comparative randomized trials of TMMC and T5-FU. In spite of large numbers of studies conducted in this area, very

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few randomized clinical trials have compared MMC and 5-FU in a parallel design, and those available did not compare subconjunctival forms of both drugs. The aim of this study was to compare the efficacy of TMMC with T5-FU in lowering IOP in high-risk glaucoma patients.

## Methods

A randomized clinical trial study was conducted in the Nikoukari Ophthalmology University Hospital, Tabriz, Iran. Forty eyes from 40 patients were enrolled. Using simple randomization in a parallel trial design, 18 patients were randomly assigned to receive TMMC and 22 to receive T5-FU. In the TMMC group, MMC was injected subconjunctivally at a dose of 0.02 mg via an 0.4 mm\*20 mm needle 180 degrees from the operating site. Likewise, 5-FU was injected into subconjunctivally at a dose of 5 mg. The inclusion criteria for this study were: 1) open angle glaucoma; 2) uncontrolled IOP; 3) optic nerve damage and visual field restriction. Patients were then followed up for measurement of IOP and development of possible complications. IOP was measured using the Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland) on 5 occasions: at baseline, 2 weeks, 1 month, 3 months, and 6 months afterwards.

The primary endpoint of the study was successful augmented surgery, defined as a consistent IOP between 6 mmHg and 22 mmHg towards the end of the evaluation period.

Data were analyzed using STATA version 11 statistical software package. Trends in IOP and IOP distributions were compared descriptively over the 6-month study. The primary endpoint was compared between the trial groups. Relative risk of treatment success for TMMC compared with T5-FU was calculated along with 95% confidence intervals (CI). Mean and median tests were also used to compare IOP between groups. Kaplan–Meier curves and survival function tests were used to assess the effect of treatment on time to success. To control possible random disproportions in some background confounders, a Cox regression model was used. All the statistical tests were interpreted on a 2-tailed basis. The test results with a *P*-value < 0.05 were considered as statistically significant. The study protocol was approved by the ethics committee of Tabriz University of Medical Sciences.

## Results

Men comprise 81% of the participants. Mean age was 67.5 years (standard deviation 10 years). The youngest subject was 48 years old and the oldest was 83 years old. Mean preoperative IOP was 30.85 mmHg. Mean preoperative IOPs in the TMMC and T5-FU groups were  $31.2 \pm 9.8$  and

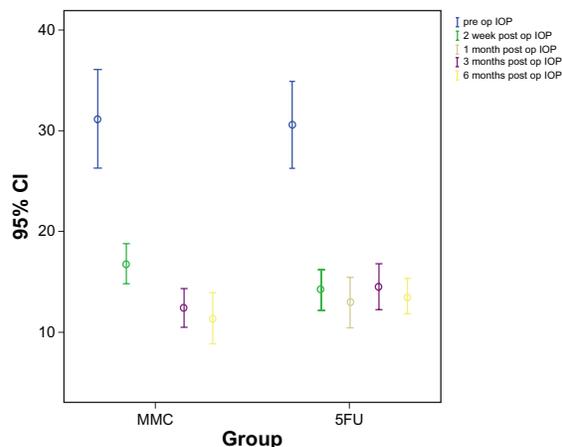
$30.6 \pm 9.9$  mmHg, respectively. Postoperatively, mean IOPs were  $11.43 \pm 4.9$  and  $13.6 \pm 3.9$  mmHg, respectively, for TMMC and T5-FU after 6 months. Figure 1 shows that average IOP in both groups began to decrease sharply during the first 2 weeks, then leveled off in the T5-FU group but continued to decrease slowly in the TMMC group.

A similar pattern of steeper IOP improvement trend was also found for the TMMC group when quartiles instead of means were compared. The distribution of IOP in the TMMC group changed from left-skewed to nearly-normal after 6 months (Figure 2).

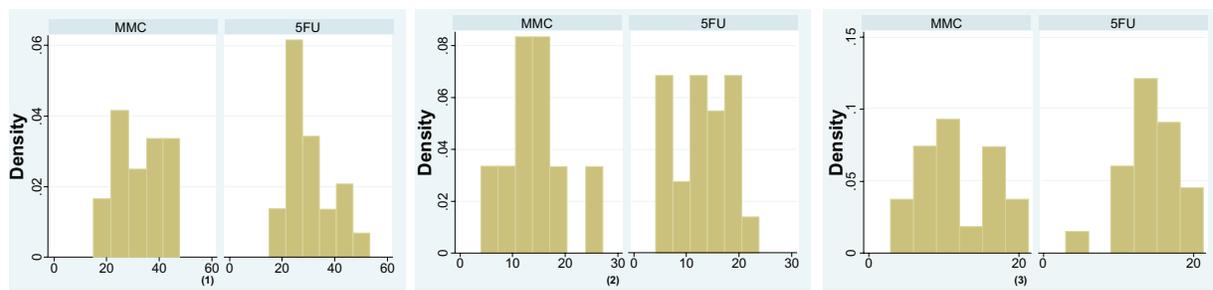
In spite of some existing descriptive differences in IOP between the groups, statistical tests showed no difference in mean and median IOP. For the primary endpoint (consistent IOP between 6 mmHg and 22 mmHg towards the end of the evaluation period), treatment was successful in 88.9% and 92.5% of subjects in TMMC and T5-FU groups, respectively. Two patients in the TMMC group and 1 patient in the T5-FU group did not have a successful outcome during the 6 months of follow-up: IOP in these 3 patients dropped to <6 mmHg, which was regarded unsuccessful. The relative risk of success for TMMC compared with T5-FU was 0.93 (95% CI: 0.8–1.1).

Testing the survival functions of successful treatment did not show any statistically significant differences between the groups (Figure 3).

The Cox regression model did not help to detect possible differences in efficacy between groups. Three cases of hypotonia (IOP < 6 mmHg) and 1 case of epithelial keratitis were observed. No differences were detected between the groups.



**Figure 1** Error bar graph (95% confidence intervals of standard errors) comparing intraocular pressure (IOP) after trabeculectomy augmented with subconjunctival mitomycin C (TMMC) versus 5-fluorouracil (T5-FU).



**Figure 2** Intraocular pressure (IOP) measured at baseline (1), 1 month (2), and 6 months (3) after surgery.

**Note:** In each histogram the left side shows the results for TMMC and the right side shows results for T5-FU.

**Abbreviations:** TMMC, trabeculectomy augmented with subconjunctival mitomycin C; T5-FU, trabeculectomy augmented with 5-fluorouracil.

## Discussion

Most of the evidence on efficacy of TMMC and T5-FU is based on studies conducted separately for these two protocols rather than comparative randomized trials. A recent review enrolled 11 placebo-controlled studies for MMC and concluded that MMC appears to reduce the relative risk of failure of trabeculectomy both in eyes at high risk of failure (relative risk 0.32, 95% CI: 0.20–0.53) and those undergoing surgery for the first time (relative risk 0.29, 95% CI: 0.16–0.53).<sup>1</sup> Another systematic review partly by the same authors conducted earlier suggested that injection of low doses of 5-FU may not be effective.<sup>2</sup> The before–after assessment of the effect of TMMC or T5-FU was quite obvious in our study although was not an objective of the study.

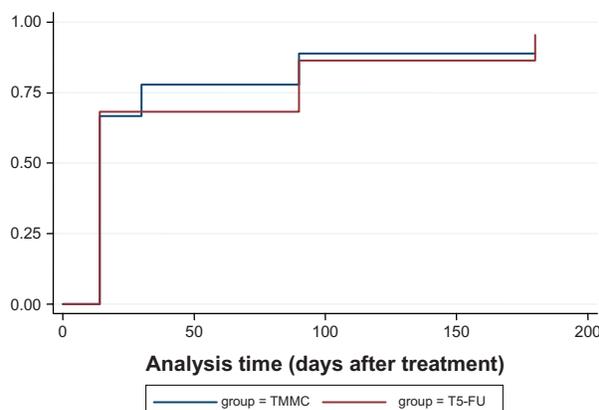
It is clear from published results that treatment protocols for augmented trabeculectomy vary widely, for example, in form of drug application (ie, injection vs sponge), application-injection site, timing, frequency, and dosage. This variation is doubled when two drugs are compared in a clinical trial. Our study was a randomized clinical trial study comparing TMMC and T5-FU. We retrieved 10 articles that

compared the two methods either in an observational study or in a parallel clinical trial design.<sup>3–12</sup> Table 1 compares the methodology of these studies.

The drugs were administered intraoperatively in most of these studies using soaked sponges. A few also used subconjunctival injection of 5-FU. Dosage and timing also differed among these studies. Nevertheless, as in our study, nearly all of these studies failed to detect statistically significant differences in success or development of complications between TMMC and T5-FU. One study found borderline statistical significance for lower mean IOP in TMMC than T5-FU.<sup>9</sup> As in our study, some of these studies stated a descriptively higher success rate for TMMC. Our study results were consistent throughout different assessment methods such as comparing means, medians, quartiles, distribution patterns, and survival methods. Most of these studies tried to test the differences between groups in complications but found no difference. However, these studies' power limits seem to be too low to enable differences in complication rates to be detected between groups. Register-based cohorts in high-income countries that have reliable patient registry databases could be a better way of answering this question. In addition case-control studies can also be a valuable way of investigating this issue in countries lacking reliable databases.

The IOP decrement pattern in our study seemed to be more transient for T5-FU than for TMMC. Khaw et al found similar results in an animal study.<sup>13</sup>

Our survival analysis using Kaplan–Meier survival comparison and survival function tests did not show a significantly longer time for TMMC to achieve success. Among the studies discussed above, Palanca-Capistrano et al found similar results as ours when using the Kaplan–Meier and survival function tests to compare TMMC and T5-FU.<sup>6</sup> Several factors are known to affect IOP, among which are corneal parameters such as corneal curvature. It is obligatory in observational



**Figure 3** Kaplan–Meier curves comparing success rate of TMMC and T5-FU.

**Abbreviations:** TMMC, trabeculectomy augmented with subconjunctival mitomycin C; T5-FU, trabeculectomy augmented with 5-fluorouracil.

**Table 1** Comparison of methods in observational and clinical trial studies comparing TMMC with T5-FU

Ref.	Design	Primary endpoint	TMMC protocol	T5-FU protocol
(12)	RCT	Achieving target IOP of 21, 18, 15, 12 mmHg	Topical MMC 0.2 mg/mL for 2 min	Topical 5-FU 50 mg/mL for 5 min
(11)	Retrospective cohort	Possible IOP mmHg	MMC 200 µg/mL for 3–5 min	5-FU 50 mg/mL for 5 min (N = 37)
(9)	RCT	Possible IOP < 15 mmHg	MMC 0.5 mg/mL for 3 1/2 min	5-FU 50 mg/mL for 5 min
(10)	Multi-center RCT	IOP	MMC 0.4 mg/mL for 2 min	5-FU 50 mg/mL for 5 min
(8)	Retrospective cohort	IOP < 21 mmHg	3–5 min exposure to 0.5 mg/mL MMC	5-FU subconjunctival injections 5 mg/0.1 mL
(3)	Retrospective cohort	IOP ≤ 21 mmHg	MMC 0.2–0.5 mg/mL for 3–5 min	5-FU 50 mg/mL for 5 min
(4)	Retrospective cohort	IOP < 21 mmHg	MMC 0.5 mg/mL for 3 min	5-FU 50 mg/mL for 5 min
(5)	RCT	IOP < 20 mmHg	MMC 0.2 mg	5-FU 5 mg subconjunctival injection
(6)	RCT	Time to IOP ≤ 21 mmHg	MMC 0.2 mg/mL for 2 min	5-FU 50 mg/mL 5 min
(7)	Retrospective cohort	IOP ≤ 21 mmHg	Intraoperative MMC	Intraoperative 5-FU

**Abbreviations:** IOP, intraocular pressure; TMMC, trabeculectomy augmented with subconjunctival mitomycin C; T5-FU, trabeculectomy augmented with 5-fluorouracil; RCT, randomized clinical trial.

studies to measure and control these parameters. Considering the effect of randomization in clinical trials, the distribution of known and unknown confounders will be random; however, it is preferable to measure these parameters, even in randomized trials.

Based on our findings and available knowledge, it appears that TMMC and T5-FU have similar efficacy in augmenting trabeculectomy. However, considering the greater, but nonsignificant, efficacy of TMMC in some studies, including ours, future larger-scale clinical trials comparing the two methods may be able to detect a significant difference. Use of subconjunctival injections of MMC and 5-FU may be recommended also because of easier methodology and possibly less procedural variation.

## Disclosure

The author discloses no conflicts of interest.

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