INTRODUCTION

It has been well established that a major risk factor for the progression of glaucomatous optic neuropathy is intraocular pressure (IOP)\(^1,2\) and that the lowest and most stable IOP with reduced diurnal variation is usually obtained by filtration surgery.\(^3\) Trabeculectomy with the adjunctive use of anti-metabolites is the most

BACKGROUND AND OBJECTIVE: To report the 5-year intraocular pressure (IOP) outcomes of patients requiring a 5-fluorouracil (5-FU) needling revision compared to a matched sample.

PATIENTS AND METHODS: Forty eyes receiving 5-FU bleb needling revision were matched to 40 patients not needled. IOP was recorded preoperatively and annually to 5 years. The main outcome measure was surgical success: IOP control without medications or surgery.

RESULTS: Thirty-two patients with 5-FU needling revision (80.0%) required anti-glaucoma medication postoperatively versus 28 control patients (70%) (\(P > .05\)). Thirty-two patients with 5-FU needling revision were complete or qualified successes compared to 36 control patients (\(P = .34\)). Eight patients with 5-FU needling revision (20%) had a reoperation versus 4 control patients (10%) (\(P > .05\)).

CONCLUSION: 5-FU needling revision can produce long-term IOP control levels similar to those who did not require the procedure. No statistically significant differences between the two groups was seen in either the use of medications or further surgery.


Five-Year Results of 5-Fluorouracil Augmented Needling Revision of Failing Blebs

Rajesh Dalvi, MD; Neil Orzech, MD, MEd; Christoph Kranemann, MD, FRCSC; Catherine M. Birt, MA, MD, FRCSC
widely accepted of the anti-glaucoma procedures and has been reported as being comparable to full-thickness surgeries in lowering the IOP in most patients with glaucoma. However, some trabeculectomy blebs fail after surgery, which may happen either in the immediate postoperative period or many years later. One national survey reported that only 67% of patients achieved an adequate target pressure 1 year after trabeculectomy. The addition of anti-metabolite treatment has improved this. The Fluorouracil Filtering Surgery Study Group reported a 74% success rate at 1 year and many reports have confirmed the usefulness of 5-fluorouracil (5-FU) in the postoperative management of the failing filtering bleb. However, most of these studies report outcomes with fairly short follow-up times. The current study was intended to examine the outcome of 5-FU needling revision after 5 years of follow-up, and to compare the outcome of the intervention to a matched group of patients whose bleb did not require the procedure.

**PATIENTS AND METHODS**

The current study was a retrospective, observational, case–control series with the aim of determining the postoperative success of trabeculectomy in patients requiring 5-FU needling revision compared to those who did not. Inclusion criteria were a history of trabeculectomy (with or without mitomycin C [MMC] and if necessary combined with cataract surgery), no previous anti-glaucoma surgery, and a minimum follow-up of 5 years. Only one eye per patient was included; for patients with bilateral surgery, each eye was independently evaluated but only one was randomly selected for inclusion in the analysis. A total of 80 patients were selected, of whom 40 were cases and 40 were controls. Cases had undergone 5-FU needling revision to their bleb in the perioperative period (range: 9 to 60 days following surgery). Control charts were selected from the total pool of patients who had undergone a trabeculectomy without 5-FU needling revision, and were matched by age, gender, and race to the cases. The age of the control patient had to match within 5 years of the case age. Race, which was self-reported, was divided into white, African, East Asian, South Asian, and Hispanic categories. Recruitment was done from two teaching hospital sites of the University of Toronto—Sunnybrook Health Sciences Centre (SHSC), Toronto, and St. Michael’s Hospital (SMH), Toronto—and the study was approved by the Research Ethics Board of each institution. Each site had a single surgeon perform all surgeries and needling revision procedures. Data collected from the chart included visual acuity before and after needling revision, anterior segment and posterior pole examinations, and gonioscopy prior to needling revision to confirm that the internal ostomy of the trabeculectomy was patent. Data for IOP and glaucoma medication use were collected before the original surgery for all patients, before and immediately after and 1 week after the 5-FU needling revision in treated patients, and at 4 and 6 weeks, 3 and 6 months, and annually thereafter to 5 years for all patients.

**Surgical Technique**

At SHSC, all procedures were done with a fornix-based conjunctival flap and 0.2 mg/mL of MMC applied for 60 to 120 seconds depending on surgical judgment (including demographic risk factors, conjunctival injection, and Tenon’s thickness), and patients were given prednisolone acetate 1% hourly while awake and then tapered depending on bleb appearance over 6 to 8 weeks. At SMH, all procedures were done with a fornix-based conjunctival flap and 0.4 mg/mL of MMC applied for 60 to 120 seconds depending on surgical judgment, and patients were given prednisolone acetate 1% hourly while awake and then tapered depending on bleb appearance over 6 to 8 weeks. Topical antibiotic and atropine 1% were used for 2 to 3 weeks at both sites.

**Bleb Revision Technique**

For all patients, an informed consent was obtained prior to the procedure. At SHSC, all patients were given xylocaine 1% topical anesthetic gel, phenylephrine 2.5%, and a topical fluoroquinolone antibiotic drop. An eyelid speculum was inserted. A 1-cc syringe was used to draw up 0.1 cc of 50 mg/mL of 5-FU (5 mg) and the plunger was drawn back to fill the hub of the 30-g needle with air. With the patient supine under an operating microscope in the treatment room, the needle was introduced under the conjunctiva slightly away from the site of the filtering bleb using a temporal approach. Once subconjunctival, the needle was advanced to the bleb margin. The needle was used to incise any Tenon’s cyst, with sideways movements of the needle to help incise the fibrosis. Egress of fluid...
and posterior extension of the bleb were taken as signs of a successful needling revision. In cases where the needling revision of the bleb did not achieve the desired results, the needle was slid below the scleral flap and the anterior chamber entered through the filtering ostomy. When aqueous flow into the bleb was seen, the needle was redirected posteriorly and the air injected. Once it was determined that the air entered the bleb and not the anterior chamber, the 0.1 cc of 5-FU was injected into and around the bleb. The eyelid speculum was removed and the patient was left supine for a few minutes. Following the procedure, the IOP and anterior chamber were assessed on a slit lamp and Seidel’s test was performed to rule out any leak. In patients from SMH, the needling revision was done in a similar fashion but with the patient sitting at a slit lamp and given 0.2 cc (10 mg) of 5-FU.

All patients were instructed to discontinue any anti-glaucoma medications (if any were used) and to take prednisolone acetate 1% every 2 hours while awake for the first 3 to 7 days, then four times daily postoperatively. Fluoroquinolone antibiotic eye drops were used four times daily after needling revision for patients from SMH. The dose for the eye drops was tapered thereafter according to the clinical appearance of the bleb. If, on follow-up visits, the bleb was found to be non-functioning, either focal digital pressure beside the bleb or inferior massage were applied to attempt to reestablish filtration. Repeat 5-FU needling revision or repeat trabeculectomy were considered in cases where the target IOP was not achieved.

**Criteria for Success**

The needling revision was considered a success if the patient obtained the individualized target IOP level with no further surgical intervention in the 5-year follow-up period and did not require anti-glaucoma medications. Target IOP levels were set based on the recommendations of Damji et al., which looked at cup-to-disc ratio and visual field defect. Early disease (cup-to-disc ratio ≤ 0.65 and mild field defect not within 10° of fixation) had an IOP target of less than 21 mm Hg and at least 20% reduction from baseline; moderate disease (cup-to-disc ratio between 0.7 and 0.85 and field defect not within 10° of fixation) had an IOP target of less than 18 mm Hg and at least 30% reduction from baseline; and advanced disease (cup-to-disc ratio ≥ 0.9 and/or visual field defect within 10° of fixation) had an IOP target of less than 15 mm Hg and at least 30% reduction from baseline. A qualified success was defined as obtaining IOP control with the use of topical medication or having a laser procedure such as argon laser trabeculoplasty or selective laser trabeculoplasty performed within the 5-year follow-up period. Patients were classified into the failure category if they underwent a surgical treatment within the follow-up period. Outcome measures were IOP decrease and number of anti-glaucoma medications relative to values before 5-FU needling revision in successful and qualified patients. Patients with a repeat 5-FU needling revision after the first injection were considered as a qualified success, but for purposes of the Kaplan–Meier analysis a repeat 5-FU needling revision was taken to be a failure, in line with other similar studies.

**Statistical Analysis**

Kaplan–Meier plots were constructed to establish the survival curves for the target pressures over time. The target pressures were determined individually for each patient, based on the level of untreated pressure and nerve and visual field damage, rather than a fixed IOP set at an arbitrary level such as 22 mm Hg. For the purposes of the Kaplan–Meier analysis, a qualified success was determined at the first visit after the needling revision or after surgery for the controls, when the IOP rose above the target IOP for that patient or when a repeated needling revision was performed. Patients requiring further surgery were classified as a complete failure.

**RESULTS**

The gender and racial distributions of the two groups were matched exactly. The average age of the patients was 67.83 ± 12.02 years in the 5-FU group and 69.68 ± 11.5 years in the control group (P > .05), indicating that the matching process was adequate. The various diagnoses of the patients and the mean preoperative medication use in the two groups are given in Table 1. The 5-FU group required slightly more medications than the control group (2.85 vs 2.65), but the difference was not statistically significant (P > .05). Although not a criterion for matching cases and controls, the number of patients with primary open-angle glaucoma was nearly the same in the two groups (27 vs 28); the distribution of secondary diagnoses also varied slightly, but the largest difference was 3 cases of second-
ary angle closure in the 5-FU group and none in the control group. The distribution of primary trabeculectomy versus combined trabeculectomy and cataract extraction was different between the two groups (22% of the 5-FU group and 55% of the control group). This difference is statistically significant (chi-square = 8.9, \( P = .003 \)) and may have occurred because only 27.5% of the patients in the 5-FU group were pseudophakic at the time of the trabeculectomy compared to 52.5% of the control patients, and this difference was also statistically significant (chi-square = 4.2, \( P = .04 \)).

The average time interval between the original filtration surgery and the needling revision procedure was 28.4 days. In the 40 patients who received 5-FU needling revision, the mean IOP was 25.5 ± 8.9 mm Hg before and 12.3 ± 6.2 mm Hg immediately following the procedure. This difference was highly statistically significant (\( t = 7.69, P < .0001 \)). The IOP of the control group at 6 weeks postoperatively was 15.3 ± 4.5 mm Hg, which was significantly lower than the IOP of the patients immediately prior to the procedure (\( t = 6.26, P < .0001 \)). The difference between the IOP level at week 6 in the control patients and the post-procedure IOP of the 5-FU group was also statistically significant, but the IOP in the 5-FU group was lower (\( t = -2.75, P = .004 \)). Of the eyes that received 5-FU needling revision, 19 had an IOP of 11 mm Hg or less immediately after injection, of which 12 eyes later required repeat injection and 7 did not. Of the remaining 19 eyes that had an IOP of more than 11 mm Hg following the injection, 12 required repeat needling revision. For two eyes, the IOP was recorded the next day and not immediately after injection. Overall, 25 (62.5%) patients had two needling revision procedures, 16 (40%) had a total of three procedures, and 11 (27.5%) had four procedures. The average time between surgery and the second procedure was 33.6 days, between surgery and the third procedure was 88.1 days, and between surgery and the fourth procedure was 44.6 days. Patients who required four procedures had the procedures done more rapidly than patients who required fewer: 9 of the 10 patients had all four interventions done in less than 2 weeks after surgery. Many of the patients who had only one procedure had it later in the postoperative course, with 8 of the 25 being later than 2 weeks.
At 5 years, the mean IOP was 15.0 ± 5.9 mm Hg in the 5-FU group, a decrease of 11.1 mm Hg (41.7%) from the preoperative level of 26.6 ± 8.4 mm Hg (t = 7.05, P < .005), and 16.3 ± 7.8 mm Hg in the control group, a decrease of 7.8 mm Hg (32.5%) from 24.2 ± 8.6 mm Hg, which was also statistically significant (t = 4.2, P < .005). However, the difference between the two groups was not statistically significant (t = -0.20, P > .05). We also examined the difference in the IOP between the patients given different concentrations of 5-FU. The lower dose group (50 mg) had a mean IOP of 17.6 mm Hg compared to 14.3 mm Hg in the higher dose group (100 mg), but this difference was not statistically significant (t = 1.72, P > .05). The Kaplan–Meier graph shows that the rate of failure in cases versus the control group was not statistically significantly different (Figure) and the level of mean IOP in each group is shown at yearly intervals in Table 2. Many patients in both groups did require supplementary topical medication. Thirty-two of the 5-FU group and 29 of the control group started taking anti-glaucoma drops again during the follow-up period, but the difference between groups was not statistically significant (chi-square = 0.62, P > .05). Of the patients who required further surgery, 8 patients in the 5-FU group and 4 patients in the control group had repeated surgery (chi-square = 0.32, P > .05). Six of the patients in the 5-FU group and 3 of the control patients started taking medications again prior to the second operation.

**DISCUSSION**

Several studies have shown that the use of postoperative injections of 5-FU improves surgical success, with the key studies reported by the Fluorouracil Filtering Surgery Study Group, which compared the outcomes of blebs treated with 5-FU to non-augmented results. Their protocol required 21 injections, with two injections given daily for the first week and then one daily for a second week given 180° away from the filtering bleb, usually in the inferior fornix. This regimen is onerous for both patient and physician, and simpler procedures were quickly developed. Postoperative bleb revision has been reported using a variety of techniques, but one of the most common is to inject 5-FU into and around a failing bleb, using the needle to incise a Tenon’s cyst and/or to elevate the trabeculectomy flap and enter the anterior chamber. This technique results in a significant salvage of filtration surgery otherwise likely to require resumption of topical medications or further surgery. Needling revision of the bleb is a technically simpler procedure than a repeat trabeculectomy, which also has an increased risk of failure compared to a primary procedure.

In our sample, resumption of medication was a common adjunct required over the 5-year follow-up period; most of the failures resumed taking medication. In most cases, the charts do not record the reason for the decision to use medications rather than a bleb needling revision; patient preference, bleb appearance, and surgeon’s judgment were some of the possibilities.

Many studies have reported outcomes with 5-FU needling revisions for failing blebs; however, the success rates for the various bleb needling procedures vary considerably, ranging from 45% at 1 year12 to 100% (complete in 58.3% and qualified success in 33.3%). A short interval between the initial surgery and needling revision has been associated with success.25,26 Our study had an average time of 28.45 days (range: 9 to 60 days) between the trabeculectomy and the first 5-FU needling revision. Earlier studies in the 1990s had a smaller number of injections done or a smaller number of eyes, with between 8 and 30 eyes being reported in various publications.15-19 Other studies had a greater number of eyes, but no control group.12,20

In view of the previous studies, the 5-FU needling revision was assumed to be an effective intervention. The question we posed was whether it was effective enough to produce long-term success and results comparable to successful trabeculectomies that had not required the needling intervention. Our study differs from those previously reported by being both case-control in format and with a minimum long-term follow-up time of 5 years, and reports a success rate of
80% (including both absolute and qualified success). Our study had an average follow-up period of 6.8 years for both cases and controls from the time of surgery compared to other studies that had a much shorter average period of follow-up. Ewing and Stamper\textsuperscript{15} had a follow-up of 9 months, whereas Shin et al. had a follow-up of 49.9 weeks from the last revision.\textsuperscript{19} Shoji et al. reported a 57.5% success rate at 5 years, but a significant difference between our study and theirs was that we report results based on individualized target IOPs and they reported the number of patients with IOP below 21 mm Hg.\textsuperscript{27} Broadway et al.\textsuperscript{9} showed a 45.5% rate of success after 5-FU needling revision compared to 80% in our study. This was presumably because the 5-FU needling revision in our study was done much earlier compared to their study, where the median interval between surgery and the first injection was 3.1 months. However, the average follow-up period after injection for their study was shorter at 20.2 months compared to 6.8 years in our study.

Our study had an age-, sex-, and race-matched group of 40 cases versus 40 controls. Matching of race was considered to be important because it is well recognized that patients of Afro-Caribbean descent have a greater tendency for poorer pressure control following surgery.\textsuperscript{28} Glaucoma is approximately four times more common in blacks than in people of European ancestry, and blindness from glaucoma is approximately six times more common in blacks. Treatment does help, but their study showed that even when treatment is identical, the risk for blacks remains significantly greater.\textsuperscript{29} In our study, both groups had 31 whites and 9 non-whites. There were 8 revision surgeries done in the 5-FU group and 4 in the control group. In the 5-FU group, 2 of the 8 revision surgeries were done in black patients, whereas 1 of the 4 revisions in the control group was done for a black patient. The proportion of the revision surgeries done in black patients was therefore the same for the two groups.

Greenfield et al.\textsuperscript{30} reported that success was more likely after one needling procedure rather than multiple procedures. However, our study did not bear out such an association. Shin et al.\textsuperscript{12} and Broadway et al.\textsuperscript{9} both identified immediate attainment of a low IOP (< 11 mm of Hg) as a factor for long-term success. However, this was not seen in our study, where patients with IOP after needling revision of 11 mm Hg or less and those with greater than 11 mm Hg had repeat injections in the same proportion (63% of both groups).

No procedure is risk free, but complications that have been reported with needling techniques are usually relatively minor; although major complications can occur, they are less common. These minor complications include small hyphema, conjunctival wound leaks, transient shallowing of the anterior chamber, and epithelial toxicity of the cornea.\textsuperscript{15,16} Of the patients who had the 5-FU needling revision in our series, two had a shallow anterior chamber that was re-formed with air and viscoelastic and one had retinal detachment. In the control group, there was one case of choroidal detachment and one case requiring anterior chamber re-formation with air and viscoelastic. Significant hypotony was seen in 3 cases after the first 5-FU needling revision, but it was transient and required no further intervention. Of these, one case later required a repeat needling revision and the other two achieved target IOPs without further intervention. Any incisional procedure carries potentially significant risk to the patient; although less invasive than a trabeculectomy or seton implantation, significant complications can still occur. Although rare, suprachoroidal hemorrhage, malignant glaucoma, and endophthalmitis have all been reported after needling procedures.\textsuperscript{30,31}

Our study has the usual shortcomings associated with a retrospective analysis. The data abstractor was not masked to the intervention used when reviewing the charts, and the clinical decision to perform a needling procedure or to reintroduce medication was taken without randomization and without a formal protocol; differences between sites may also have introduced a confounding factor into the study. However, the study validates the clinical practice at the two hospitals with respect to the use of 5-FU as a primary intervention in preference over a trabeculectomy revision. The fact that the two sites used different techniques both in the study procedure (dose and patient position) and the actual surgery does add possible confounding factors. The fact that no statistically significant differences were found between the two sites nevertheless suggests that the procedure is robust to these differences, and allows one to more easily generalize the outcomes to other practices.

Bleb needling revision can usually be performed in an office setting and, with experience, is fairly simple to perform, although different clinicians may find one protocol easier to perform than the other. It is also repeatable and relatively safe. Serious complications are
always a possibility, but based on these data and others, the incidence is lower for bleb needling revision than for trabeculectomy.\textsuperscript{22,a,b} If necessary, a trabeculectomy can be repeated after the needling revision is done because needling revision preserves the remaining conjunctiva. These factors make bleb needling revision the first incisional procedure of choice in the setting of a failing bleb. Furthermore, surgical revision of a bleb or a completely new surgery is more technically demanding with an increased risk of failure.\textsuperscript{22,a,b} At 5 years postoperatively, the mean IOP had decreased significantly compared to preoperatively in both groups and the difference between the two groups was not statistically significant. Thirty-two patients in the 5-FU group had a outcome defined as either a complete or a qualified success compared to 36 patients in the control group and this difference was not statistically significant. Hence we can safely assume that the intervention of needling revision was effective enough to produce results comparable to trabeculectomies that were uncomplicated and did not show bleb failure.

Our study demonstrates that performing a 5-FU needling revision to a failing filtering bleb can improve trabeculectomy success rates to levels similar to those found in our control group, thus reducing the need for a repeat surgical procedure along with its associated risk factors.

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