

A REVIEW OF THE EFFECT OF 5-FLUOROURACIL ON THE OUTCOME OF TRABECULECTOMY IN IBADAN

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SUMMARY

Aim: To retrospectively assess the outcome of trabeculectomy performed using an intraoperative sponge soaked in 5-fluorouracil (50 mg/ml).

Methods: Trabeculectomy with an intraoperative sponge soaked with 5-fluorouracil (5-FU) was performed in 21 eyes of 14 patients. The reduction in intraocular pressure (IOP), complications and variations in visual acuity were noted.

Results: The mean preoperative IOP was 31.5 ± 10.6 mmHg. The mean postoperative IOP was 7.3 ± 5.7 mmHg on the second postoperative day and 17.5 ± 9.8 mmHg at 3 months. Postoperative complications were mostly transient, with 33% of eyes requiring postoperative antiglaucoma therapy to reduce IOP. Visual acuity improved postoperatively in 3 eyes, worsened in 9 eyes and remained the same in 9 eyes.

Conclusion: Even though a small study, an intraoperative sponge soaked with 5-FU seems to be a safe and effective adjunct to trabeculectomy.

Key words: 5-fluorouracil, trabeculectomy, glaucoma, Nigerian

INTRODUCTION

Glaucoma is more prevalent among blacks than whites.^{1,2} It assumes a more aggressive course in blacks,³ and is a major cause of blindness in many African countries with black populations.^{4,7} In developing nations, especially those with black populations, surgical treatment of glaucoma is generally assumed to be preferable to medical treatment.^{8,9} The main cause of failure of filtering surgery is scarring of the filtering bleb.¹⁰

Fluorouracil, originally found to inhibit intravitreal scarring through its inhibitory effect on fibroblasts,^{11,12} was efficacious after filtering surgery in cases where

filtering surgery had previously failed,¹³ in cases of aphakic glaucoma,^{14, 15} and in cases of inflammatory glaucoma.^{15, 16}

Recent studies have also found it to be efficacious in eyes that have not undergone previous surgery,¹⁷⁻¹⁹ and in low-tension glaucoma.²⁰

Complications due to subconjunctival 5-FU injection have been described.^{21,22} They include corneal epithelial defects, conjunctival wound leaks, and possible globe perforation. In addition, the need for repeated administration causes the patient some discomfort and limits its use. This has prompted various studies to investigate the intraoperative use of 5-FU, which is felt to be safer than mitomycin C.¹⁹ The advantages of the single intraoperative administration are that: (i) the drug is applied directly to the surgical site where it is most needed; (ii) it is only administered once, allowing for a smaller total dosage; and (iii) there is no patient discomfort or the inconvenience of frequent clinic visits for injections.¹⁹ This study was undertaken to determine the results of a single dose administration of 5-FU during trabeculectomy in Nigerian patients who had previously been on medical therapy.

PATIENTS AND METHODS

All patients with glaucoma who had undergone trabeculectomy with intraoperative use of 5-FU at the University College Hospital, Ibadan were included in the study. Data was collected retrospectively from their case notes and included age; type of glaucoma (on gonioscopy); eye operated; intraocular pressures at presentation, preoperative and postoperative (at 2 days, 1 month, 3 months, 6 months and last clinic visit). Other data collected included visual acuity (preoperative and one month postoperative), follow-up period postoperative, complications (intraoperative and post operative), and additional antiglaucoma drugs utilized postoperative.

The technique of trabeculectomy was generally considered to be Watson's²³ modification of Cairn's²⁴

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technique combined with the Luntz modification.²⁵ The conjunctival flap was either fornix-based or limbal-based. A 4 x 5mm piece of surgical sponge (Weckcel sponge) saturated with 5-FU (50mg/ml) was placed on the sclera. The conjunctiva and Tenon's capsule were then pulled over the sponge which was resaturated every minute with a drop of 5-FU for a total of 5 minutes,²⁶ taking care not to touch the free-cut edge of the conjunctiva with the soaked sponge. After the sponge was removed, the area was irrigated copiously with 20ml of normal saline. The trabeculectomy was then completed with a rectangular superficial scleral flap incision (5 x 4 mm) and a deep corneo-scleral block excision (3 x 3 mm). A peripheral iridectomy was made before closing the superficial scleral flap with 8/0 virgin silk; the conjunctiva was also sutured with 8/0 virgin silk. Subconjunctival gentamycin (20mg) and depomedrol (0.3ml) were injected into the inferior fornix, followed by topical chloramphenicol and atropine drops before the eye was padded. Post-operative antibiotic, mydriatic and steroid drops were utilized. Four consultant ophthalmic surgeons performed the surgeries.

RESULTS

Trabeculectomy, using an intraoperative sponge soaked in 5-FU, was performed on 26 eyes. Of these, 5 were excluded from the study as the patients were lost to follow-up immediately after discharge from hospital following their trabeculectomy. Only 21 eyes of 14 patients were, therefore, available for the study. The

mean age of the 14 patients was 41.6 ± 13.5 years, ranging from 24-72 years. There were 15 male and 6 female patients. Twelve of the 21 eyes were right eyes while 9 were left eyes. On gonioscopy, most of the eyes (18) were found to have chronic open angle glaucoma, while only 3 eyes had chronic narrow angle glaucoma.

The presenting intraocular pressure (IOP) ranged from 13-55mmHg, with a mean of 31.5 ± 10.6mmHg. Postoperative IOP on day 2 ranged from 0-25mmHg, with a mean of 7.3 ± 5.7mmHg. Table 1 shows that on the second postoperative day, 90.5% of the eyes (19 eyes) had a postoperative IOP of 18mmHg or less, while 2 eyes had an IOP of 25mmHg. At 3 months, the postoperative IOP ranged from 4-52mmHg (mean 17.5 ± 9.8mmHg), and at the last clinic visit, the mean IOP had risen to 20.3 ± 9.8 mmHg (table 1).

The length of follow-up ranged from 3 months to 4 years (mean of 2.8 ± 1.05 years); most of the patients (76%) followed-up for more than 1 year. Complications are presented in table 2 with the most common postoperative complication being shallow anterior chamber, which occurred in 7 eyes (33%). The only case of hypotony at 6 months in 1 eye had resolved by the next visit. Seven eyes (33%) required postoperative antiglaucoma medication to reduce the IOP; timoptol, pilocarpine and diamox were used. Of the 7 eyes, 2 required only one drug, 2 eyes required 2 of the 3 drugs, while 3 eyes required all the 3 antiglaucoma drugs.

Table 1. Intraocular pressures

Cases	Initial	Pre-op	2 Days Post-op	1/12	3/12	6/12	Last Visit
1.	32	22	25	12	17	17	17
2.	16	21	10	30	24	24	24
3.	18	23	8	18	10	10	10
4.	26	27	0	8	10	16	18
5.	21	20	0	8	4	6	10
6.	44	26	10	22	16	10	10
7.	36	27	12	16	33	26	14
8.	30	30	5	15	12	18	18
9.	32	26	6	14	15	15	10
10.	52	16	18	24	18	10	18
11.	31	17	6	5	19	14	17
12.	37	20	7	14	14	15	13
13.	35	19	3	15	15	18	24
14.	36	21	6	10	10	13	10
15.	38	16	4	10	11	9	10
16.	55	30	7	16	18	18	18
17.	30	33	4	24	15	16	20
18.	24	31	2	13	52	40	33
19.	13	22	5	4	20	14	22
20.	28	20	8	17	16	18	26
21.	28	26	8	31	18	20	22
Success Rate			90.5%	76.2%	85.7%	85.7%	71.4%

Table 2. Complications of Trabeculectomy with 5-FU

Complications	Number	Percentage (%)
Shallow anterior chamber	7	36.8
Hypotony (at 6 months)	1	5.3
Increased IOP	3	15.8
Hypaema (intraoperative)	2	10.5
Cataract	2	10.5
Small pupil	1	5.3
Ptosis	1	5.3
Encapsulated bleb	1	5.3
Peripheral anterior synechiae	1	5.3
Total	19	100.0

Note: Some eyes had more than one complication.

Only one patient developed encapsulated bleb. Needling of the bleb was performed with subconjunctival injection of 5-FU.

Visual acuity improved postoperatively in 3 eyes (2 eyes improved by 1 line, while 1 eye improved from counting fingers to 6/12), worsened in 9 eyes (7 eyes dropped 1 to 2 lines, the other 2 had advancing cataracts). The rest had the same visual acuity pre and postoperative.

DISCUSSION

The drug, 5-FU, was first introduced to ophthalmology by Blumenkrantz in 1982 for the treatment of experimental vitreoretinopathy.¹² 5-FU is a fluorinated pyrimidine analogue that inhibits fibroblast proliferation by competitive inhibition of thymidylate synthetase.²⁶ It has since gained wide acceptance as a useful antiproliferative agent in trabeculectomy. Initially, the use of antimetabolites was reserved for those patients thought to be at high risk of surgical failure from postoperative scarring of the trabeculectomy bleb. However, now that the dosage and risk profile of 5-FU have been assessed, more surgeons feel more comfortable using the treatment in lower-risk patients, in the hope of further improving the success rate for this group.²⁷⁻²⁹ The advantages of intraoperative application of 5-FU over its administration as postoperative injections appear to include less frequent patient visits, no risk of ocular perforation, no corneal epithelial abnormalities, and decreased discomfort to the patient.^{17,19}

A concentration of 50 mg/ml was chosen for the sponge because of the known efficacy of this dosage in postoperative application, especially in blacks.^{17,30} The initial results reported by Lanigan et al.³¹ were encouraging, with a success rate of 91% (100% if the results of only the low to moderate-risk category were considered) with limited follow-up (3-9 months).

In this study, the success rate at 6 months was 85.7% (18 eyes having IOP < 21mmHg). In the first year of follow-up of the Fluorouracil Filtering Surgery Study (FFSS),¹⁴ there was a 73% success rate in patients with moderate to high-risk characteristics compared to a 50% success rate for the control group. In a black population from Ghana, Singh et al.³⁰ reported a success rate of 73% (IOP < 21mmHg). Similarly, Egbert et al.¹⁷ had shown an 83% success rate in a black population with a mean follow-up of 282 days. In this small study, the success rate was 85.7% at 3 months and at 6 months (qualified success where IOP was 21 mmHg or less with additional medical therapy were included). The follow-up period in this small group ranged from 3 months to 4 years (mean 2.8 ± 1.05 years).

At the last visit (4 years in 3 eyes), the success rate had dropped dramatically to 71.4% from the 85.7% at 6 months. This coincidentally had been reported by the FFSS group,¹⁴ where the 5-year follow-up reported a drop in the success rate to 49% from a 73% success rate at 1 year. It seems that the short-term success rate in terms of IOP control using 5-FU is quite good. Long-term follow-up, however, suggests that after 2 years, the success rate falls,³² presumably due to slowly replicating fibroblasts.

Khaw et al.³³ in the rabbit model, showed that five-minute intraoperative exposure to 5-FU had a temporary delaying effect on fibroblast outgrowth, whereas mitomycin C displayed longer-lasting effects and may, therefore, be more appropriate in high-risk cases.

In this study, postoperative visual acuity was the same as preoperative visual acuity in 9 eyes, worsened in 9 eyes and improved in 3 eyes (2 eyes improved by 1 line while 1 eye improved from counting fingers to 6/12). Of the 9 eyes with worsened visual acuity, only 2 eyes dropped more than 2 lines, both due to advancing cataracts. Cataract is a well-known complication of trabeculectomy, probably secondary to the hypotony induced by the surgery. In a study by Watson,³⁴ it was found that many patients complained of an alteration in vision in the weeks following glaucoma surgery, but that it usually recovered fully within 6 weeks. Cunliffe et al.³⁵ also showed in their study that visual acuity started to return to preoperative levels by the third postoperative week, from which point no eye showed a deterioration in corrected visual acuity of more than one Snellen line.

Complications in our small series were mainly transient (68.4% of complications), the most common being shallow anterior chamber in 7 eyes (33%). The 2 eyes with cataracts later had cataract surgery, and the encapsulated bleb had needling of the bleb with subconjunctival 5-FU injection using the Allen et al. method.³⁶

Late complications of postoperative 5-FU injections, including an increased risk of endophthalmitis and

possible late bleb breakdown, may also be expected with this method, due to the occurrence of more ischaemic and thin bleb structures than with standard trabeculectomy.³⁷ None of our cases developed either of these complications.

CONCLUSION

This study has shown that in the short-run, the adjunctive use of 5-FU during trabeculectomy is relatively safe and effective in lowering IOP in patients who belong to the high-risk group for failure of trabeculectomy, because of their African descent. In the long term, however, the drop in success rate will need to be investigated further and solutions proffered.

The limitations of a case series apply to our results. There were no controls, nor was there any masking of patient or physician. A larger study with controls and double masking is therefore suggested, to come up with more concrete evidence of long-term efficacy of the use of 5-FU in the eyes of black people.

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