

Outcomes of Trabeculectomy with 5-Fluorouracil at a Nigerian Tertiary Hospital

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Purpose: To report the outcomes of trabeculectomy with adjunctive 5-Fluorouracil (5-FU) at a Nigerian tertiary hospital.

Methods: In this prospective study, all patients with glaucoma undergoing trabeculectomy with 5-FU at the University College Hospital, Ibadan, Nigeria, from June 2009 to May 2010 were enrolled. Each patient had a complete ophthalmic evaluation. Intraocular pressure (IOP), visual acuity (VA) and complications post-trabeculectomy were assessed at one year. Success of the procedure was defined as complete when no additional medications were required to achieve an IOP of ≤ 18 mmHg, or qualified when additional medications were required to achieve the same goal.

Results: A total of 47 eyes of 31 patients with mean age of 48.9 ± 19.6 (range 14-77; median 52) years including 21 (67.7%) male subjects underwent trabeculectomy with 5-FU. Mean presenting IOP was 31.8 ± 12.2 mmHg. Mean deviation (MD) on Humphrey visual fields was -15.9 ± 9.7 dB with the majority of the patients (18 subjects 58.1%) presenting with advanced glaucoma based on MD worse than -12 dB and severe glaucomatous optic neuropathy (cup to disc ratio of 0.9-1.0). At 1 year postoperatively, 95.1% achieved qualified success while 83% had complete success.

Conclusion: This prospective study adds to the existing knowledge that trabeculectomy with 5-FU is effective at controlling IOP in Nigerian patients.

Keywords: Trabeculectomy; 5-fluorouracil; Nigeria

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INTRODUCTION

Glaucoma is the most common cause of irreversible blindness, both worldwide^{1,2} and in Nigeria.³ The prevalence of glaucoma has been reported to be highest in St Lucia⁴ and in West Africa.⁵ This is consistent with the higher prevalence seen in people of African descent

living in North America and the Caribbean.⁶ The majority of glaucoma in people of African descent is primary open angle glaucoma (POAG) which often presents at an earlier age.⁷ It is associated with higher IOP and more rapid progression. Presentation occurs late in the course of the disease, with up to 50% of patients already blind in one eye at presentation.^{5,7,8-10}

Trabeculectomy is more effective at lowering IOP than both medical and laser treatment in Africans.^{6,11} The advantage of surgery becomes more evident in Sub-Saharan Africa, where the cost of medical treatment is high and often unaffordable. Therapeutic issues are further complicated by poor compliance and the unavailability of medications.

The Advanced Glaucoma Intervention Study (AGIS)¹¹ and the Collaborative Initial Glaucoma Treatment Study⁶ (CIGTS) reported a higher incidence of failed trabeculectomy among people of African descent as compared to Caucasians. This may be due to increased keloid formation in the former race, predisposing them to increased scarring with resultant bleb encapsulation and failure.¹² In a study performed in Ibadan, Nigeria, bleb encapsulation was the most common late complication following trabeculectomy.¹³

Studies on the outcomes of trabeculectomy in Nigeria have been mostly retrospective.¹³⁻¹⁶ This prospective study reports the outcome of trabeculectomy and evaluates the efficacy of active bleb management with the use of intra- and postoperative subconjunctival 5-fluorouracil (5-FU) in Nigerian patients.

METHODS

In this prospective study, all patients with glaucoma scheduled for primary trabeculectomy with 5-FU at the University College Hospital, Ibadan, Nigeria from June 2009 to May 2010 were followed and their information was entered into a standard surgical outcome data sheet at each visit. Patients with juvenile open angle glaucoma (JOAG), primary open angle glaucoma (POAG), and primary angle closure glaucoma (PACG) were included. Patients with congenital glaucoma, secondary glaucoma and patients who had previous trabeculectomy were excluded. The main indication for surgery in these patients was uncontrolled IOP despite maximum tolerable medications. Two patients opted for surgery due to financial constraints to continue with medications.

Each patient underwent a complete history and ophthalmic evaluation consisting of uncorrected and best corrected visual acuity,

slit lamp examination, IOP measurement by Goldmann applanation tonometry, and gonioscopy using a 4 mirror Posner gonioscope. All patients with open angles were dilated and stereoscopic examination of the vitreous, retina and optic nerve head was performed with a 78-diopter lens. Patients with occludable angles were dilated after a laser peripheral iridotomy was performed.

Automated full-threshold perimetry was performed for subjects with best-corrected visual acuity better than 6/60 using the 24-2 SITA standard program on the Humphrey 740 Visual Field Analyzer (Dublin, California, USA). All visual field results included were reliable based on the reliability criteria of the Humphrey Field Analyzer II User's Guide (Humphrey Instruments Inc., San Leandro, California, USA).

Preoperative data included age, gender, and duration of glaucoma medication use, type of glaucoma, preoperative IOP, visual acuity, presence of lens opacity, cup to disc ratio (CDR), and preoperative mean deviations on Humphrey visual fields.

The study adhered to the tenets of the Declaration of Helsinki. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this study.

Surgical Procedure

All surgical procedures were performed by 2 surgeons (OO and AO) either within 4 weeks of presentation or on failure of medical treatment. All eyes underwent trabeculectomy with a fornix-based conjunctival flap. Prior to the procedure, normal saline was injected into the subconjunctival space with a 26G needle to create a potential space for aqueous drainage and allow a large area for antimetabolite treatment. After a peritomy was created, blunt dissection of the conjunctiva was performed 10-12 mm posteriorly and laterally without radial incisions at the sides. A rectangular scleral flap 4×5 mm in size was then dissected leaving uncut sclera 1 mm behind the limbus (the vertical sides of the rectangular scleral flap did not extend over the limbus), to encourage posterior flow of aqueous.

Five pieces of 3x3 mm cellulose surgical sponges saturated with 5-FU (50mg/ml) were placed in the subconjunctival area for 5 minutes. Tenon's capsule and conjunctiva were pulled over the sponges carefully to avoid contact of the free conjunctival edge with 5-FU-saturated sponges. The sponges were then removed and the surgical site was thoroughly irrigated with 20 ml of normal saline. A rectangular sclerostomy and a peripheral iridectomy were performed after paracentesis. The scleral flap was closed with two 10-0 nylon sutures at the edges of the flap. The conjunctiva was closed with three 10-0 nylon sutures using a purse-string technique. A watertight bleb was ensured at the end of surgery.

Postoperative Care

All patients were placed on hourly topical steroids (generic dexamethasone) during waking hours for a minimum of 6 weeks, which was tapered off over 3-4 months. They were also placed on antibiotic and diclofenac sodium eye drops four times a day, and atropine twice a day.

Patients were actively and promptly monitored for bleb function and appearance, and intervention was performed whenever necessary. Subconjunctival 5-FU at a dose of 7.5 mg was injected 6 mm posterior to the bleb in patients with moderate to severe vascularization in the first 3 months (early postoperative period). The diagnosis of moderate and severe vascularization was determined using the Indiana grading system.¹⁷ Other interventions such as digital bleb massage, trans-conjunctival needling in combination with subconjunctival 5-FU were performed as necessary. Transconjunctival needling was performed on patients with encapsulated blebs. This was a sterile procedure performed under topical anesthesia with a 30G needle. The needle was introduced subconjunctivally about 2mm posterior to the bleb and advanced to puncture Tenon's capsule and lift the scleral flap. The needle was carefully moved from side to side breaking the episcleral adhesions until the bleb was reformed. After this procedure, 7.5 mg of 50 mg/ml of 5-FU was injected about

6 mm posterior to the bleb. Bleb massage was performed as necessary by the surgeons during clinic visits. This was done by applying digital pressure to the globe through the upper eyelid behind the posterior lip of the scleral flap. All of these interventions were performed in the clinic at the slit lamp. Postoperatively, all patients were seen weekly for 4 weeks and every 2 weeks over the next 8 weeks. After 3 months postoperative visits were scheduled as needed.

Outcome Measures

The primary outcome of interest was IOP, measured by Goldmann applanation tonometry, within 48 hours, one month, three months and one year postoperatively. Secondary outcomes included postoperative complications and interventions after surgery. Early postoperative complications including shallow anterior chamber, elevated IOP and hyphema, and late complications, such as encapsulated blebs, cataracts and corneal decompensation were also documented.

Surgical success was defined as complete when no additional medications were required to achieve an IOP of ≤ 18 mmHg or qualified when additional medications were required to achieve the same goal. A second IOP cut off of ≤ 16 mmHg was also used to define the outcomes.

Additionally, we evaluated the use of intraoperative and postoperative subconjunctival 5-FU, frequent topical steroidal and non-steroidal medications, suture removal, trans-conjunctival needle revision and bleb massage among these patients. Cataract progression was assessed with the WHO adaptation¹⁸ of the Lens Opacity Classification III System¹⁹ pre- and post-trabeculectomy.

Data Analysis

Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS; IBM Corp., New York, NY, USA) version 16. Chi-square test for discrete variables was used between variables and the student t-test was used

to compare mean pre- and post-operative IOP. P values <0.05 were considered as statistically significant.

RESULTS

During the study period, 292 patients with mean age of 56.5±16.6 years including 162 (55.5%) male subjects presented with glaucoma. A total of 47 eyes of 31 patients underwent trabeculectomy with 5-FU. Mean age of operated patients was 48.9±19.6 (range 14-77, median 52) years including 21 (67.7%) male subjects. Forty-five (95.7%) eyes had POAG and two eyes had PACG. Table 1 shows the demographic and clinical characteristics of patients.

Mean presenting IOP was 31.9±12.2 (median 28, range 12-66) mmHg. Average mean deviation on Humphrey visual fields was -15.9±9.7 (median -13) dB. The majority of patients (18

cases, 58.1%) presented with advanced damage based on mean deviation worse than -12 dB and severe glaucomatous optic neuropathy (cup-to-disc ratio of 0.9-1.0). All patients were on anti-glaucoma medications preoperatively. Mean duration of medication use was 11.5±10.6 months and the mean number of glaucoma medications was 2.3±0.74 preoperatively.

Postoperative Intraocular Pressure

Mean IOP within 48 hours postoperatively was 8.29±6.35 (median 6) mmHg. At 4 weeks postoperatively, mean IOP increased slightly to 9.42±3.71 (median 10) mmHg. Mean reduction in IOP from preoperative values was significant (95%CI: 18.8-26.0 mmHg, P<0.001); mean preoperative IOP was 31.9 mmHg, mean post-operative IOP at 1 year was 12.3 mmHg and mean difference was 19.6 mmHg. Table 2 details IOP at different postoperative visits.

One year postoperatively, 39 (83%) eyes achieved complete success defined as IOP ≤ 18 mmHg and 35 (74.5%) eyes had complete success defined as IOP ≤ 16 mmHg. Qualified success with IOP ≤ 18 mmHg was achieved in 45 (95.7%) eyes while qualified success with IOP ≤ 16mmHg was achieved in 38 (80.8%) eyes. Six (12.8%) eyes were started on a single medication (latanoprost) to control IOP and one eye required a combination of timolol and latanoprost.

Active bleb management using subconjunctival 5-FU was performed in 9 (19.1%) eyes. Four eyes had 3 consecutive doses and 5 eyes had 2 consecutive doses of postoperative sub-conjunctival 5-FU. Out of these 9 eyes, 7 eyes had IOP <12mmHg one year postoperatively. Bleb massage was performed in 32 (68.1%) eyes.

Early postoperative complications included shallow anterior chamber in 6 (12.8%) eyes.

Table 1. Preoperative demographic and clinical characteristics

	N (%)
Age	
≤40 years	9 (27.3)
>40 years	24 (72.7)
Sex	
Male	22 (66.7)
Female	11 (33.3)
Duration of anti-glaucoma medications use	
≤12 months	34 eyes (72.3%)
>12months	13 eyes (27.7%)
Mean duration: 11.5±10.6 months	
Median duration: 9 months	
Range: 1 – 60 months	
Pre-operative IOP (mmHg)	
≤21mmHg	10 eyes (21.3%)
22-30mmHg	16 eyes (34.0%)
31-70mmHg	21 eyes (44.7%)
Mean IOP: 31.9±12.2 mmHg	
Median IOP: 28 mmHg	
Range: 12-66 mmHg	

IOP, intraocular pressure; N, number

Table 2. Intraocular pressure changes

Intraocular pressure	Mean (mmHg)	SD	Median	Range (mmHg)	95% CI	P value*
Preoperative IOP	31.9	12.2	28.0	12-66		
1 day PO	5.3	3.7	4.0	0-16	13.7 (22.6-30.4)	<0.001
3 months PO	11.5	4.5	10	2-28	10.9 (16.6-24.1)	<0.001
6 months PO	11.6	4.2	11	5-28	11.1 (16.7-24.1)	<0.001
1 year PO	12.3	4.4	11	5-28	9.5 (15.9-24.0)	<0.001

SD, standard deviation; CI, confidence interval; IOP; intraocular pressure; PO, post-operation

*compared to preoperative IOP

Table 3. Postoperative complications

	Number of eyes (%)
Early postoperative complications	
Shallow anterior chamber	6 (12.8)
Hyphema	7 (14.8)
Elevated IOP	2 (4.2)
Late postoperative complications	
Elevated IOP	2 (4.2)
Encapsulated blebs	2 (4.2)
Cataract	8 (17.0)

IOP; intraocular pressure

Three of these eyes had small bleb leaks and were managed conservatively with a torpedo pressure patch while the remaining three eyes with overfiltration underwent anterior chamber reformation with injection of viscoelastic material in the operating theater. Intraoperative hyphema was noted in 7 (14.8%) eyes. These patients were managed conservatively in the Fowlers position with topical steroids and atropine and there was complete resolution of the hyphema in one week. Cataract progression was noted at one year in 8 (17.0%) eyes. Bleb encapsulation was noted in 2 eyes. One of these patients was started on medications and the other patient underwent bleb revision leading to successful IOP control. There was no case of endophthalmitis. Postoperative complications are summarized in Table 3.

Preoperative visual acuity ranged from 6/6 to light perception (LP). Postoperatively, visual acuity remained in the same range. At one year, eight (17.0%) eyes experienced a significant drop in visual acuity defined as loss of two or more Snellen lines. Cataracts were responsible for the decrease in visual acuity in these eyes.

DISCUSSION

Management of glaucoma in Sub-Saharan Africa is challenging. Medical management has been considered impractical due to the high cost of long term medication, compliance with medical therapy and the need for regular follow up.^{12,20} Compliance is further worsened by the psychosocial problems due to inappropriate health beliefs.

Although a number of studies^{12,21,22} have shown that African race is one of the risk factors for failure of glaucoma filtration surgery,

trabeculectomy remains the most common glaucoma procedure in Nigeria. The Advanced Glaucoma Intervention Study (AGIS Report 9)¹¹ demonstrated that after failure of medical therapy, the chance of surgical failure (IOP>18 mmHg and diminution of visual acuity) is slightly higher in black patients as compared to white patients if trabeculectomy is performed first. This may be due to increased keloid activity predisposing to scarring, bleb encapsulation and failure.

The current study demonstrated the efficacy of trabeculectomy with antimetabolites and active postoperative bleb management in reducing IOP among Nigerians. This was evidenced by mean IOP reduction exceeding 50% from baseline values one year postoperatively. Previous studies on trabeculectomy with or without antimetabolites in Nigerians reported complete success rates of 61-73.3%, where success was defined as IOP ≤ 21 mmHg.^{23,24} These were retrospective studies and had a high rate of loss to follow up. A previous study from Ibadan, Nigeria,¹³ reported success in 79.4% of patients, but this report did not categorize patients into qualified and complete success.

In the present study, 5-FU was used in all patients. 5-FU is a pyrimidine analogue antimetabolite which blocks DNA synthesis and inhibits fibroblast proliferation.²⁶ Several studies have demonstrated the effectiveness of antimetabolites in enhancing the results of glaucoma filtration surgery.^{16,23,24,26} Adegbehingbe et al²³ reported a better outcome in patients who underwent augmented surgery with 5-FU as compared to those who received unaugmented surgery. Ashaye et al¹³ however, reported no difference in surgical outcomes between patients in whom 5-FU was used as compared to those not receiving this antimetabolite. Although it may be difficult to draw conclusive evidence from these studies because of their retrospective nature, there is considerable evidence that intraoperative use of 5-FU improves the probability of maintaining low IOP.²⁷⁻²⁸ The use of antimetabolites is more relevant in Africans who have a higher predisposition to scarring and bleb failure. Adjunctive use of antifibrotic agents such as

mitomycin C or 5-fluorouracil at the site of surgery significantly reduces the risk of bleb failure.²⁹

The majority of patients in this study had advanced glaucoma and therefore required low target IOP to preserve their visual field. The AGIS³⁰ showed that in advanced glaucoma, irrespective of race, patients with an IOP consistently <18 mmHg had the least chance of visual field progression. Therefore, the goal in our study was to achieve IOP \leq 18 mmHg. In this study, 83% of our patients had IOP \leq 18 mmHg at one year follow up.

Approximately 27% of the patients were <40 years of age in this study. This is similar to the report by Verrey et al³¹ in Ghana and Adegbehingbe et al²³ in Nigeria. African patients usually present late in the course of the disease, with up to 50% of cases already blind in one eye at presentation.⁵

A high proportion of our patients required some form of bleb manipulation. This may be due to the need to achieve a low target IOP as mentioned above since a large proportion of our patients had advanced disease. Topouzis et al³² reported a high rate of bleb manipulation in a study on eyes with advanced glaucoma undergoing trabeculectomy. The incidence of postoperative shallow anterior chamber was slightly lower in our study than reports from other studies.^{13,16} This may be due to the conjunctival suturing technique. In the current series, there was no clinically documented case of choroidal effusion/detachment, the incidence of which is very low among blacks as compared to Caucasians. Singh et al³³ did not find any case of hypotony or choroidal detachment in their study on West Africans. It has been suggested that this could be due to greater scleral rigidity in black subjects. Scleral rigidity has been hypothesized as a factor in the pathogenesis of hypotony maculopathy.³⁴ Hypotonic maculopathy is more common among young and myopic patients. These 2 groups of patients have low scleral rigidity which may facilitate the inward collapse of the sclera wall in hypotony. The sclera in young people has more elasticity and flexibility than older patients and therefore may contract more in hypotony.³⁵

Blebitis and endophthalmitis are established complications of trabeculectomy; however, there were no such cases in our series. Filtration surgery with adjunctive antimetabolite is associated with a higher risk of endophthalmitis (0-5%)^{27,28} than conventional unaugmented trabeculectomy (0-0.4%).^{36,37} The absence of infectious complications in the current series may be explained by the routine preoperative measures of ensuring negative conjunctival culture and the use of povidone-iodine to sterilize the conjunctival fornices. We also used very stringent aseptic techniques intraoperatively and frequent antibiotics were employed postoperatively. All patients were adequately counseled and educated perioperatively.

The incidence of encapsulated blebs was relatively low in our patients as compared to the report by Ashaye et al¹³ in an earlier study in Ibadan. This may be due to active bleb management in the early postoperative period. At one year in this study, cataract was responsible for drop of vision in 17% of patients. This is low compared to the risk of cataract reported by Stead et al³⁸ and the AGIS study (approximately 50%).³⁹ Stead et al reported that 28 patients (27%) had cataract surgery postoperatively while 4 declined to undergo surgery despite being indicated. The total number of patients who had cataract post-trabeculectomy (operated or not) in the study was 32 (30.8%).³⁸ However, follow-up period was much longer in these studies.

Limitations of this study include the relatively short follow up period of one year and inability to report visual field changes at one year due to uncorrected refractive error and lenticular opacities. This study however adds to the existing knowledge that guarded filtration surgery is effective in controlling IOP in Nigerians. Active bleb management provides better IOP control and the reoperation rate following trabeculectomy was low in this study. As surgical results continue to improve, acceptability of glaucoma surgery by patients may improve in Nigeria.

Conflicts of Interest

None.

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