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Trabeculectomy with intraoperative 5–fluorouracil in Enugu, South-Eastern Nigeria: A pilot study.

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SUMMARY

AIM: To determine the outcome of 5-FU applied at time of trabeculectomy in Nigerian patients with open-angle glaucoma who had primarily received medical therapy. Patients were 13 adult Nigerian seen consecutively in the Glaucoma Clinic between September, 1996 and November, 1997. All had open-angle glaucoma and had primarily been treated with topical antiglaucoma therapy. None required a combined surgical procedure and they were on their topical antiglaucoma therapy except Pilocarpine until the day of surgery. Each patient was followed up for at least 3 months. The surgical technique was similar to cairns: Just prior to raising the scleral flap 15mg/0.3ml of full strength 5-FU on cotton-wool swab was applied to the sclera for 5 minutes with or without apposition of the conjunctival flap over the swab. This was followed by copious irrigation with normal saline and then raising of the limbal based partial-thickness scleral flap. With at least a 3-month postoperative follow-up 10 out of 14 eyes had a final intraocular pressure of <18.5mmHg. 4 required additional subconjunctival 5-FU. The final visual acuity remained unchanged in 10 eyes while 3 recorded a worsening of visual acuity of more than 2 snellen lines due to progression of cataract. The postoperative complications included bleb breakdown and leakage, early and late bleb fibrosis, choroidal detachment and chronic hypotony. Neither endophthalmitis nor extinction phenomenon was recorded in our study. Trabeculectomy with intraoperative application of 5-FU is relatively safe and effective but a larger study with a longer follow-up is required to determine the long-term success rate and complications of this technique.

KEY WORDS: ***5–Fluorouracil, Nigeria, open-angle glaucoma, trabeculetomy.***

INTRODUCTION

With the introduction of trabeculectomy by Cairns and other in the late sixties[1–4] the management of patients with glaucoma was significantly modified. This surgical method was developed in response to a need for a safe and predictable method of lowering the intraocular pressure. It appears to have a relatively high success rate with low incidence of complications.[5,6] The earlier surgical techniques were full of hazards and consequently they were preferably carried out late in the disease process, when maximum medical therapy had failed, often after many years and when devastating visual loss had already occurred. Comparatively, with the acceptance of trabeculectomy surgical intervention started being carried out at an earlier stage in the disease progression. Its implementation as a primary procedure (i.e. prior to medical therapy) has now been suggested and some developing countries through necessity have already introduced "surgery first in glaucoma" even before its worldwide acceptance as a standard approach to glaucoma.[7]

On the long-run trabeculectomy is superior to medical treatment. It alone, can consistently lower the IOP to that level at which good visual prognosis in terms of field loss is achieved.[8] It is more cost-effective and the quality of life of patients who undergo surgery is superior to that of those receiving medical therapy who require daily drop therapy and more frequent hospital follow-up visits.[9]

However, in spite of the high success rate recorded with trabeculectomy in various studies (i.e. when it is strictly defined on the basis of IOP control without the need for postoperative medication), when the results of trabeculectomy in black patients are included there is a great variation in success rate. In

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black African patients with primary open-angle glaucoma the success rate of filtration procedures has been reported to be as low as 39% two years postoperatively.[10] Berson and associates reported that young black patients have a worse success rate than older black patients after trabeculectomy. It was found that the black African initially did well after surgery, but in a few weeks, the IOP rose again and drainage blebs disappeared or became isolated as pigment blocked the iridectomy and scar tissue the scleral wound.[11] Compared with the Caucasian eye the reaction to trauma has been stated to be more severe in the Negro eye. There is a high incidence of scar tissue formation in these too.

Yet, there is evidence from the U.S.A. and Caribbean countries that chronic glaucoma is a more severe disease in people of African origin than Caucasians.[12] Blindness from chronic glaucoma has been reported to be eight times more common in non-white populations, registered blind in the U.S.A.[13,14]

The disease is commoner, has an earlier onset, is more resistant to medical and laser therapy and is more aggressive, resulting in blindness more frequently and at a younger age in black than in white patients.[15]

In parts of West Africa where trachoma does not exist glaucoma is perhaps second only to cataract in causing blindness. The disadvantages of medical therapy are well known. Surgical therapy is, therefore, a better alternative but carries the risk of complications and failure.

The routine use of adjunctive 5-fluorouracil (5–FU) and mitomycin-C has increased the success rate of trabeculectomy in the developed world. In a prospective trial in a black West African population intraoperative topical 5-FU application has been shown to increase significantly the success rate of trabeculectomy.

To assess the outcome of trabeculectomy with intraoperative 5-FU in Nigerian patients with open-angle glaucoma who had primarily received medical therapy, we analysed the result in the 14 eyes of 13 patients in whom this technique was used. The analysis was for final IOP level and visual acuity at least 3 months postoperatively.

To the best of our knowledge this is the first study in Enugu to assess the outcome of adjunctive use of 5-FU during trabeculectomy.

PATIENTS AND METHODS

From September, 1996 to November, 1997, trabeculectomy was performed with adjunctive 5-FU application on 14 eyes of 13 consecutive patients who had been diagnosed to have open angle glaucoma.

All patients included in the study were drawn from the Glaucoma Clinic of UNTH, Enugu. The thirteen (13) patients who were included:

* Were Nigerian adults
* Had received primary medical treatment following diagnosis of glaucoma
* Did not have a combined trabeculectomy and cataract surgery
* Were followed up for at least 3 months postoperatively
* Were receiving all their antiglaucoma therapy except pilocarpine until the day of surgery. Pilocarpine eye-drops were stopped at least a month before surgery.

All patients provided informed consent and the use of 5-FU in association with trabeculectomy was approved by the Ethics Committee of the University of Nigeria Teaching Hospital Enugu.

The surgical techniques used by the two surgeons in the study were similiar. The technique was similar to that by Cairns.

A conjunctival flap which was either fornix- or limbal-based was raised. After haemostasis of the episclera was attained with the thermal cautery point the size of the scleral flap to be raised was marked out but not pierced. This measured about 4mm x 3mm. 5-fluorouracil was applied on the sclera for five minutes with a cotton-wool swab that was cut to match the size of the sclera to be raised. The cotton-wool swab is prepared by the surgeon Just before the application of 5-FU. It is of moderate thickness to allow the conjunctiva stretch over it as much as possible avoiding the edge. 0.3ml of 250mg/5ml solution of full strength 5-FU is dropped onto the cotton-wool with syringe. Each surgeon used his discretion to decide whether to appose the conjunctiva over the cotton-wool swab or not. Where the conjunctival edge would lie on the cotton-wool swab the surgeon applied the cottonwool swab on the sclera only. The 5-FU was, however, applied to both the sclera and subconjunctival whenever the conjunctiva edges did not lie directly on the cotton-wool swab. After five minutes the cotton-wool swab was removed and the entire area thoroughly irrigated with normal saline. A 4mm x 3mm limbal based partial-thickness scleral flap was dissected into clear cornea. A 1mm x 1mm corneal block was removed and a peripheral iridectomy performed. The scleral flap was closed with

two to three interrupted 8/0 virgin silk sutured. The conjunctival flap when limbal-based was sutured by using either continuous or interrupted 8/0 virgin silk sutures. When fornix-based, two wing sutures were applied at the edges after tight apposition of that conjunctiva over the ornea about 1mm anterior to the limbus.

Subconjunctival injections of 20mg of Genticin and 2mg of Dexamethasone were administered in the inferior fornix. Topical Atropine 1%, Betnesol-N and Terracortril ointment were instilled into the eye on the Operation table before padding it. Postoperatively, the patient was placed on:

* Guttae Atropine 1% t.d.s.
* Guttae Betnesol-N 2 hourly x 48hrs then q.d.s. except where it was necessary to continue intensive topical steroid therapy for a longer period
* Oc. Terracortril
* Caps Indocid 25mg t.d.s. x 1/52 or
* Caps Feldene 20mg dly x 1/52

Other topical medications that could be included depending on the findings on examination included:

* Guttae Phenylephrine 2.5%
* Guttae chloramphenicol/OC. chloramphenicol

The topical steroids are usually continued for up to two months postoperatively.

The patients are examined one, two, three, eleven, eighteen days postoperatively and then one, two, three, four months postoperatively unless complications were encountered and more frequent visits necessary. At each postoperative visits, patients had:

* Slit-lamp examination
* Visual acuity assessment
* IOP measurement
* Bleb appearance assessment

The operation was considered a complete success when the IOP was <18.5mmHg using Schiotz tonometer with 7.5g weight, a qualified success when the IOP was ≥ 18.5mmHg but ≥ 21.9mmHg, a qualified failure when IOP was 3 21.9mmHg but ≥25.8mmHg and a complete failure when it was >25.8mmHg and the patient required topical medications.

Every patient included in the study was followed up for at least 3 months postoperatively.

RESULTS

Information regarding age, sex, preoperative and postoperative IOP is summarised in table 1.

There were 7 males and 6 females. 6 out of the 13 patients had associated systemic disease: 1 was both hypertensive and diabetic, 3 hypertensive only, 1 diabetic and the last akochs patient. All the patients were primarily treated with topical medications, 6 for < 1 year before surgery and the rest for 1 year. The mean period of postoperative follow-up was 6 months (range: 3 months –1 year).

When a postoperative IOP of ≤ 18.5mmHg was considered a success 12 of 14 eyes had successful outcome. When, however, the criterion was IOP of < 18.5mmHg 10 out of 14 eyes were said to have had successful surgery. Only 1 out of the 14 eyes was on topical medications at the final follow-up due to the complete failure of the surgery. The only case of qualified failure recorded an IOP of 25.8mmHg one year after surgery.

The preoperative central visual acuity ranged from 6/9 to CF, 9 out of the 14 eyes had preoperative visual acuity of ≥ 6/18. Following surgery 3 of the 14 eyes had worsening of visual acuity of more than 2 snellen lines as a result of the chronic hypotony or progression of cataract.

The visual acuity was unchanged in 10 patients.

Table 1: ***Baseline patient information***

SEX (NUMBER):	
* Male	7
* Female	6
AGE (YEARS):	
* Mean	50
*Range	32–77
IOP (mmHg) WITH SCHIOTZ TONOMETER (7.5G)	
* Preop:	
– Mean	28
– Range	15.6 – 30.4
* Postop (≥ 3 MONTHS)	
– Mean	16.1
– Range	5.0 – 30.4

Table 2: ***Postoperative visual acuity***

POSTOP VISUAL ACUITY	NUMBER OF EYES
improved > 2 lines	1
NO CHANGE	10
WORSENED > 2 LINE	3

No case of extinction phenomenon was recorded. The worse preoperative visual acuity of counting fingers in our study was retained after surgery.

Table 3 lists postoperative complication recorded in our study.

Table 3: ***Postoperative complications***

	NUMBER OF EYES
EARLY COMPLICATION (≥ 1 MONTH):	
* BLEB BREAKDOWN	1
* BLEB FIBROSIS	2
* ANTERIOR CAPSULAR CATARACT	1
* CHOROIDAL DETACHMENT	1
* HYPOTONY MACULOPATHY	1
LATE COMPLICATIONS (> 1 MONTH)	
* BLEB FIBROSIS	2
* PROGRESSION OF CATARACT	3
* HYPOTONY	1

One of the patients had a bleb breakdown within the first postoperative week which required subconjunctival injections of autologous blood. There were the associated positive Seidel test, flat anterior chamber and hypotony. Development of anterior capsular cataract followed reformation of the anterior chamber.

Two of the eyes that had early bleb fibrosis with rising IOP (≥18.5mmHg) first had ocular massage but when the lowering of IOP was not sustained by the next follow-up visit, were given subconjunctival doses of 0.1ml (5mg) 5–FU daily for three consecutive days. This was followed by lowering of IOP to level < 18.5mmHg with associated avascular, thin cystic filtering blebs. The two cases of later fibrosis manifested raised intraocular pressure (> 18.5mmHg) 6 and 10 weeks postoperatively, respectively. Due to the hypervascularity around the bleb in one of the eyes the patient was given two doses of 0.1ml subconjunctival 5-FU on two consecutive days. (A third dose was not possible because the patient had to return to his place of work outside the town). The outcome was unsuccessful. In the second eye there was no evidence of ongoing inflammatory process on or around the bleb at the time the raised IOP was recorded therefore no subconjunctival 5-FU was given. The surgery was a complete failure.

The lenticular opacities observed in three eyes in the preoperative period became denser in the late postoperative period with associated worsening of visual acuity of > 2 snellen lines.

The only case of choroidal detachment in our study responded to oral steroids.

None of the eyes in our study developed early or late endophthalmitis.

DISCUSSION

5-fluorouracil is an antimetabolite. It has the ability to inhibit conjunctival fibroblast proliferation thereby preventing scarring of the filtration bleb after exposure to the filtration site. It acts by inhibiting DNA synthesis and acting selectively on the S-phase (synthesis phase) of the cell cycle.[25] Fibroblastic attachment and migration are unaffected by 5-FU. This antimetabolite shows a delayed inhibitory effect on cell proliferation compared to that following use of mitomycin-C suggesting that the drug may first be converted into more active metabolies.

Due to the recent reports of significant improvement in the success rate of trabeculectomy following the use of antiproliferative agents, we carried out a pilot study aimed at determining the outcome of intraoperative use of 5-FU during trabeculectomy on adult Nigerian patients with open-angle glaucoma and on primary treatment with topical medications. This group constitutes a significant number of patients seen in the Glaucoma clinic and one with even a higher risk of failure following routine trabeculectomy. The two outcome measures studied were intraocular pressure and visual acuity complications were studied to determine the safety of the drug. Intraocular pressure (IOP): The mean final postoperative IOP in our study was 16.1mmHg. This agreed with the finding in the Ghanaian study by Singh et al. [26]

Four (4) of the eyes in our study received additional subconjunctival 5-FU in the presence of bleb fibrosis. This was not the case in the Ghanaian study. This difference is likely due to some differences in techniques and dosage of the 5-FU used. While the Ghanaian study used 50mg/ml of full strength 5-FU we used 15mg/0.3ml.

The conjunctiva was apposed over the 5-FU soaked sponge in all patients in the Ghanaian study while this was not the case in our study. The decision to appose the conjunctiva over the 5-FU soaked cotton wool swab depended on the surgeon's discretion which was guided by how protected the conjunctival edge would be from contact with the 5-FU solution. Again,

all the patients in our study were primarily treated with topical antiglaucoma medications for varying lengths of time (range: 3 months - 25 years).

Evidence has accrued implicating chronic preoperative topical therapy as a risk factor for failure of filtration surgery. It is proposed that chronic therapy with combination topical therapy has adverse effects on the conjunctiva and postoperative wound healing.[27] Of the 14 eyes with at least a 3-month postoperative follow-up, 12 had a final postoperative IOP of less than or equal to 18.5mmHg.

At an IOP level of ≤18.5mmHg there is a good visual prognosis in terms of field loss for the glaucoma patient. Evidence from pooled analysis of several different studies of glaucoma filtration surgery have shown that the lower the final intraocular pressure after surgery (even within the range 19–15mmHg), the better the visual prognosis in terms of field loss.[9] However, it is now known that there are patients in whom IOP seems to play little or no role in progressive damage. Apparent visual stability, even over a period of years, may not be causally related to treatment.

In the short term, 5-Fluorouracil has been shown to enhance the 29 success rate of medium term IOP control in 'high risk' eyes. However, long term follow-up of eyes treated in this way suggests that after 2 years the success rate falls,[30] presumably due to slowly replicating fibroblasts.

A large study among the blacks with a longer period of postoperative follow-up is needed to provide information on the long-term success rate of trabeculectomy with intraoperative 5-FU.

Visual acuity: In our study the visual acuity returned to the pre-operative levels in 10 eyes within 6 weeks while 3 had deterioration of vision of more than 2 snellen lines. This worsening of vision was largely due to progression of cataract which would have been as a result of the normal ageing changes or probably secondary to the hypotony induced by the surgery.

A large percentage of patients have a subjective change in vision following routine trabeculectomy and it is important to warn them of these possible changes as operations are often performed on eyes with normal acuity. Watson[31] stated that many patients complained of an alteration in vision in the weeks following glaucoma surgery, but that it usually recovered fully within 6 weeks. Cunlife et al[32] demonstrated in their study that visual acuity started to return to pre-operative levels by the third postoperative week, from which point no eye showed a deterioration in corrected visual acuity of more than one line of snellen.

Complications: Every operation on the eye carries some risk. With adjunctive use of 5-FU during trabeculectomy the antimetabolite has its own potential complications. However, compared with mitomycin- C, at clinical concentrations, 5-FU causes temporary inhibition of fibroblast proliferation with late recovery after single application[33] 5-FU has a much less severe effect than MMC.

One case of bleb breakdown and leakage was recorded in our study. This is one of the documented potential complications of 36 antimetabolities. Treatment consisted of a failed attempt at surgical repair, subconjunctival injection of autologous blood, cessation of topical steroids and increased dosage of oral vitamin C. When the Seidel test eventually became negative the anterior chamber was reformed with air and within a week following that the visual acuity returned to pre-operative level. An anterior capsular cataract, however, complicated the latter procedure.

Wound leaks and bleb leaks following filtration surgery with antimetabolite are more likely to heal slowly because of the relative absence of fibroblastic activity.

An attempt at surgical repair of the conjunctiva failed because of the friable nature of the tissue resulting from the application of the 5-FU. Non-surgical measures were then taken to encourage healing.

Blood has been evolved to speed and enhance healing. Khaw et al have shown that specific growth factors present in the blood can even reverse the effects of powerful antiscarring agents on ocular fibroblasts.[37-38]

Ascorbic acid functions in the formation of collagen[39] which is important for wound healing.

Steroids impair wound healing so stopping its use postoperatively would encourage wound healing response.

Early bleb fibrosis occurred in two of the eyes for which each was given subconjunctival injections of 0.1ml (5mg) 5-Fluorouracil in the quadrant adjacent to the bleb. This complication was suggested by excessive conjunctival inflammation and a rising intraocular pressure for which postoperative injections of 5-FU can be given in conjunction with the intra-operative agents.[40]

(a) The efforts to create a permanent opening (during trabeculectomy) is not physiological because the

normal biologic response to injury is wound healing with formation of a scar. Several factors conspire against establishing a patent fistula and conjunctival filtering bleb in the first few weeks after surgery. However, the most common cause of bleb failure after trabeculectomy is the healing response leading to the sealing of the surgical fistula by fibrovascular proliferation at the episcleral surface along the edges of the scleral flap.

(b) Experimental studies have suggested that the maximal fibroblastic proliferation around the fistula occurs between 3 and 7 days postoperatively. Clinically, the most problematic period is between the first and fourth weeks. By 6 weeks, it is usually clear whether or not the procedure will succeed.

Giving of postoperative subconjunctival 5-FU on manifestations of signs of bleb fibrosis would augment the effect of the intraoperative application.

A diagnosis of hypotony maculopathy was made in one of the patients from history after a period of unresolving symptoms and associated diminution in vision. She started complaining of metamorphopsia and positive scotoma in the field of view of the operated eye from the tenth postoperative day. Direct ophthalmoscopy revealed nothing and fluorescene angiograpahy was not available. This patient who was both hypertensive and diabetic was also found to have ignorantly continued instilling Guttage Timoptol on the operated eye, for about four weeks after surgery. Following filtration surgery excess subconjunctival aqueous run-off, conjunctival leak, uveal effusion and cyclodialysis cleft may lead to hypotony.

Many eyes will tolerate relatively low pressures indefinitely without sequelase, but others become soft enough to develop macular and/or disc oedema, among other signs like cataract, choroidal folds and so on. The same patient eventually had progression of cataract which led to the deterioration of her vision of more than 2 snellen lines. This was the case also in two other eyes which had preoperative early cataract.

The only case of choroidal detachment in our study was associated with IOP of less than 5mmHg. Choroidal detachment usually follow a suprachoroidal effusion which results form hypotony. No patient in our study developed early or late blebitis or endophthalmitis.

Limitations of our study include

* Small size
* Difference in extent of areas of application of 5-FU. Some ideally had antimetabolite applied to both sclera and subconjunctival while others had to the sclera only.
* Use of Schiotz Tonometer instead of the more accurate Goldman's applanation tonometer in measuring the IOP
* Intraoperative application of lower concentration of 5-FU
* The short duration of the study.

Despite all the limitations of our study ten out of fourteen eyes (71%) achieved successful outcome (IOP <18.5mmHg) after at least a 3 month follow-up.

This is considered a success and would even be more so if the result lasts for a longer period, on the other hand, without treatment in this population, many eyes are likely to degrade to a visual acuity of no light perception. Furthermore, studies in Ghana[26] suggest that there is a great difference in rate of trabeculectomy success with 5-FU as compared to without an antimetabolite. It is, therefore, suggested that essentially all trabeculectomies in black West African patients should be augmented intraoperatively with an antimetabolite. The choice of antimetabolite will depend upon availability, cost and surgeon preference. 5 -FU:

* Is relatively less expensive (approx £1.00 per ampoule of 250mg/5ml)
* Can be stored in solution for a longer duration of time.
* Produces temporary inhibition of fibroblast proliferation and has less severe effects than MMC, thus often less intimidating to the novice glaucoma surgeon. From one study 5-FU is relatively safe.

CONCLUSION

Despite the added risk with antimetabolite use, among black West Africans where there is a high prevalence of glaucoma as well as high risk of failure of glaucoma filtration surgery, alternative therapies for the treatment of advanced glaucoma namely medical treatment and trabeculectomy without antimetabolite are not as effective or are very expensive. Antimetabolite trabeculectomy currently seems the most satisfactory treatment option for glaucoma in West African black patients who usually present in the advanced stage.

This study has shown that, in the short term, the adjunctive use of 5-FU during trabeculectomy is relatively safe and effective in lowering IOP.

RECOMMENDATIONS

(1) A case-control study is needed to compare the pressure-lowering effect of trabeculectomy with intraoperative 5-FU and that without in Nigerian glaucoma patients.

(2) This study is a useful pilot study for a larger study. A lot of information is still needed on antimetabolite trabeculectomy. Longer follow-up will reveal long-term success rate and greater complications of trabeculectomy with 5-FU.

(3) In the absence of the ideal surgical sponge which is more absorbent, to still ensure that at least 25mg of 5-FU in 1ml is absorbed, a cotton-tipped applicator like the 'ear cotton-bud' could be used instead of ordinary cotton-wool swab which easily drips with fluid.

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