



## A STUDY ON INTRAOPERATIVE USE OF 5-FLUOROURACIL IN HIGH RISK GLAUCOMA FILTRATION SURGERY.

**Dr. Roopa R. Naik**

MBBS, MS (Ophthalmology), Professor & HOD, Dept. of Ophthalmology, Dr. Vikhe Patil Memorial Hospital, DVVPF's Medical College, Vilad Ghat, Ahmednagar

**Dr. Siddharth B. Sane\***

MBBS, Junior Resident (Ophthalmology), Dr. Vikhe Patil Memorial Hospital, DVVPF's Medical College, Vilad Ghat, Ahmednagar \*Corresponding Author

### ABSTRACT

Glaucomatous eyes with previously failed filtration surgery, young patients, previous inflammation, neovascularisation, previous intraocular surgery, trauma are high risk cases for failure of filtration surgeries. Adjunctive use of antimetabolites has been shown to increase success rate in high risk Glaucoma filtration surgery. Various complications by postoperative use of 5-FU prompted the study to investigate the intraoperative use of 5-FU in high risk cases of Glaucoma.

**Materials and Methods:** A prospective, comparative study of single, intraoperative use of 5-FU in 40 patients of high risk for Glaucoma filtration surgery.

**Results :** None of the patients developed corneal epitheliopathy, hypotony maculopathy or endophthalmitis. Minor non sight threatening complications like shallow AC (responded to pressure patching) and hyphaema (underwent spontaneous resolution) were noted in 9 and 2 patients respectively.

**Conclusion:** Intraoperative 5-FU is safer and more effective as compared to postoperative injection.

**KEYWORDS :** Intraocular pressure, Bleb, Anti Metabolites.

### INTRODUCTION

The aim of glaucoma filtration surgery is to normalise the intraocular pressure (IOP) by creating a fistula which allows controlled egress of fluid from the eye. Any surgical trauma in the body is followed by protective mechanisms of inflammation and wound healing response. Proliferation of fibroblasts, production and remodelling of collagen constitute a mechanical barrier to filtration.

Glaucomatous eyes with previous failed filtration surgery, young patients, previous inflammation, neovascularisation, previous intraocular surgery, trauma are high risk for failure of filtration surgeries.

The adjunctive use of anti-metabolites has been shown to inhibit wound healing and increase success rate in high risk Glaucoma filtration surgery.<sup>(1,2)</sup>

Several studies have demonstrated that postoperative subconjunctival injection of 5-fluorouracil (5-FU)<sup>(1-4)</sup> and a single intraoperative application of Mitomycin-C (MMC), an alkylating agent<sup>(5,6,7)</sup> are effective in minimising scar formation and promoting successful filtration surgery.

However both of these agents are fraught with numerous complications. Postoperative subconjunctival 5-FU injection may cause corneal epithelial defects, conjunctival wound leaks and globe perforations. MMC might cause wound leaks, hypotony maculopathy, sclera thinning, cataract, and late endophthalmitis. These complications prompted this study to investigate the intraoperative application of 5-FU.

### MATERIALS AND METHODS:

The study was intended to investigate the following aspects:

1. Efficacy in high risk Glaucoma filtration surgery.
2. Comparison of low dose (25 mg/ml) and higher dose (50 mg/ml) of 5-FU.
3. Safety profile of intraoperative use of 5-FU

A prospective, comparative study of single, intraoperative application of 5-FU in 40 patients of glaucoma who were at high risk for failure of filtration surgery was done to determine the aforementioned aspects.

### Inclusion Criteria:

1. Previously failed filtration surgery.
2. Congenital / Juvenile Glaucoma.
3. Pseudophakic / Aphakic Glaucoma.
4. Glaucoma secondary to Uveitis.
5. Traumatic Glaucoma.
6. Advanced Primary Angle Closure Glaucoma.
7. Advanced Primary Open Angle Glaucoma.

The patients were divided into 2 groups - A & B, each of 20 eyes. 5-FU was used in concentration of 25 mg/ml in group A, while 50 mg/ml in group B, for a period of 4 minutes. Preoperatively all routine examinations including Best Corrected Visual Acuity (BCVA), IOP measurements and gonioscopy were conducted.

**Operative Procedure:** A modified Cairns Trabeculectomy was performed in all patients. After proper informed consent, peribulbar block was given. Using a superior rectus bridle suture, a limbal based conjunctival peritomy was done with 8 mm cord length conjunctival incision, 8-10 mm posterior to surgical limbus. A partial thickness rectangular scleral flap, 4 mm wide and 3 mm long was dissected anteriorly into clear cornea. A 4x4 mm cotton pledget soaked in 5-FU was placed over scleral flap for 4 minutes. Flap margins were kept away from the pledgets. The area was then copiously irrigated with about 30 ml of RL solution. A 2x2 mm inner Scleral window was dissected and excised. A peripheral iridectomy (PI) was performed. Scleral flap was sutured with 2 "10-0" Mersilk sutures. Subconjunctival injection of Gentamycin and Dexamethasone (0.5 cc each) was given at the end of surgery.

**Postoperative Regimen:** Topical Dexamethasone (0.1 %) QID with Tobramycin (0.3 %) QID. Suture lysis was not performed in any patients. Anti-Glaucoma medications were added after 1 month if IOP was considered to be too high.

**Follow up:** Patients were followed up on day 1 and 7 and then 1 month, 3 months, 6 months, 9 months postoperatively. At each visit the following details were examined:

1. BCVA
2. IOP
3. Anterior Chamber

4. Bleb morphology
5. Other complications

**Criteria for Success:** At the end of 1 year the patients were divided into 3 groups as follows:

1. Complete success: IOP < 21 mm Hg without any anti Glaucoma medications.
2. Qualitative success: IOP < 21 mm Hg with anti Glaucoma medications.
3. Failure: IOP > 21 mm Hg anti Glaucoma medications

Statistical analysis was performed using Student-t Test.

**RESULTS:**

**Patients and Eyes –**

We studied 40 eyes of 40 patients, who underwent trabeculectomy with intraoperative use of 5-FU.

**Table 1 - Sex**

	Grp. A	Grp. B
Age (yrs)	41.25 +/-21.36 (Range 1-68)	39.5+/-20.04 (Range 1-72)
Male : Female	11:9	11:9

Both groups were matched for age of patients (P=0.39).

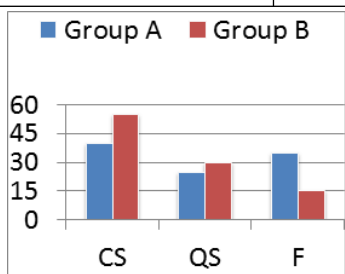
**Table 2 - Preoperative parameters**

	Grp. A	Grp. B
PreOp IOP	39.95 +/- 9.8 mmHg	40.9 +/-9.49 mmHg
PreOp Drugs	2.5 +/-1.05	2.5 +/- .96
Risk Factors	6+ <sup>1</sup>	8+ <sup>1</sup>

There was no statistically significant difference in preoperative IOP (p=0.42), preoperative number of drugs (p=0.37) and risk factors (p=0.35) between the two groups.

**Table 3 - Diagnosis based Distribution**

Diagnosis	Grp. A	Grp. B
PACG with past filtration surgery	1	4
POAG with past filtration surgery	2	4
Pseudophakic / Aphakic Glaucoma	5	2
Congenital Glaucoma	4	3
Neovascular Glaucoma	3	1
Traumatic Glaucoma	1	1
Chronic Uveitis	2	2
Advanced PACG	0	1
Advanced POAG	2	2



**Graph 1 - Success percentages**

Complete success (CS) in Group A was 40% with 25% qualified success (QS) while 35% failed (F). Complete success in group B was 55% with 30% qualified success while 15% failed. Overall success in Group A was 65% and group B was 85%.

The fall in IOP in whom the surgeries were successful in group A at end of 1 year was 53.2% while in group B was 56.7%. There was a significant fall in IOP in both groups with no significant difference between the 2 groups (p=0.1).

In failed surgeries, initially there was adequate IOP control but later there was a steady rise in IOP even with medications.

Both groups showed improvement in Visual Acuity of about one line (Snellen's Chart). Approx. 6/60 - 6/36.

**Table 4 - Bleb Morphology**

Morphology	A			B		
	CS	QS	F	CS	QS	F
Diffuse, avascular.	8	3	-	9	4	-
Cystic, avascular.	-	2	2	2	2	2
Cystic, vascular	-	-	5	-	-	-
Encapsulated	-	-	-	-	-	1

Table 4 shows all patients (100%) with a diffuse, avascular bleb were successful while there was 10.% failure with a cystic vascular bleb.

Patients with POAG past filtration surgery, advanced POAG, pseudophakic Glaucoma and Aphakic Glaucoma in both groups showed 100% success rate (CS+QS).

Patients with Congenital Glaucoma in Group A showed 100% failure rate while only 1 out of 3 in group B showed complete success. In patients with Neovascular Glaucoma, there was 100% failure rate in group A while only 1 patient showed qualified success in group B.

**Table 5 - Postoperative complications**

Complication	Grp. A (n=20)	Grp. B (n=20)
Shallow AC	4	5
Hyphaema	2	0
Choroidal Detachment	0	2
Corneal epitheliopathy	0	0
Cataract Progression	2	2
Hypotony maculopathy	0	0
Giant encapsulated bleb	0	1
Endophthalmitis	0	0

Cataract progression was seen 2 out of 10 phakic eyes (20%) in group A and 2 out of 16 phakic eyes (13%) in group B. Choroidal Detachment was seen in 1 patient of group B which resolved spontaneously with conservative management. Giant encapsulated bleb was seen in 1 patient of group B with subsequent failure.

Minor non sight threatening complications like Shallow AC (responded to pressure patching) was seen in 4 and 5 patients in groups A and B respectively; while Hyphaema (resolved spontaneously) was seen in 2 patients in group A.

**DISCUSSION:**

The advantages of intraoperative application of 5-FU over postoperative injection includes less frequent patient visits, no risk of ocular perforation, no corneal epithelial abnormalities and decreased patient discomfort (Dietze et al<sup>8</sup>, Lanigan et al<sup>9</sup>)

Our success rates (CS + QS) of 85% in group B (5-FU, 50 mg/ml) are comparable to success rates of 73-96 % in other studies using postoperative 5-FU injections (Patitsas et al<sup>10</sup>, Singh et al<sup>11</sup>, Vijaya et al<sup>12</sup>), or when intraoperative application was combined with postoperative injections (Smith et al<sup>13</sup>)

The IOP lowering effect in groups A and B was 53.2% and 56.7% respectively. These are slightly higher than 42% reduction of IOP reported by Bell et al<sup>14</sup> with use of 25 mg/ml concentration of 5-FU and 49% reported by Vanourakin et al<sup>15</sup>. MMC showed a higher IOP lowering effect ranging from 56-70 %<sup>15,16</sup>. Our study showed a increase in the mean IOP

There were no corneal complications in either group while

Parrish and Hever et al<sup>17</sup> have reported 55% incidence of corneal epitheliopathy after postoperative 5-FU injections. No cases of hypotony maculopathy were seen in any of the 40 patients. However Bell et al<sup>14</sup> have reported 4% incidence of hypotony maculopathy with 5-FU (25 mg/ml) and Huang PT<sup>18</sup> has quoted a incidence of 4-10 % following the use of 0.4 mg/ml MMC.

Two out of ten patients (20%) in group A and two out of sixteen patients (13%) in group B showed Cataract progression while slightly higher rate (27%) was reported by Dreyer et al<sup>19</sup> with use of both 5-FU and MMC.

An incidence of 11% and 8% of bleb leaks following use of MMC and 5-FU respectively has been reported by Smith et al<sup>20</sup>. However, no bleb leaks during follow up over 1 year were seen in our study. However, late bleb leaks and endophthalmitis may occur later due to more ischaemic and thin bleb structure than standard trabeculectomy<sup>21</sup>. Thus there were certain limitations to our study. 12 months may not be adequate to determine long term success nor late complications.

### CONCLUSION:

1. 5-FU intraoperatively is safer and more effective as compared to postoperative injection.
1. 5-FU in both concentrations has a lesser IOP lowering effect as compared to MMC.
2. 5-FU (25 mg/ml) should be the anti metabolite of choice in pseudophakic Glaucoma.
3. 5-FU in both doses is not effective in Congenital Glaucoma.
4. 5-FU (50 mg/ml) is more effective, but also has higher complication rate than 5-FU (25 mg/ml).

### REFERENCES:

1. The Fluorouracil Filtering Surgery Study Group. Fluorouracil Filtering Surgery Study One Year follow up. Am J Ophthalmol 1989; 108:625-35.
2. The Fluorouracil Filtering Surgery Study Group. Three years follow up of Fluorouracil Filtering Surgery Study. Am J Ophthalmol 1993; 115:82-92.
3. Krug JH Jr, Melamed S. Adjunctive use of delayed and adjustable low dose 5 Fluorouracil in refractory Glaucoma. Am J Ophthalmol 1990; 109:412-18.
4. Wantanabe J, Jwala K et al. Trabeculectomy with 5-Fluorouracil. Acta Ophthalmol 1991; 69:455-61.
5. Chen CW, Huang HT, Blair JS, Lee CC. Trabeculectomy with simultaneous application of Mitomycin-C in refractory Glaucoma. J. Ocul. Pharmacol 1990; 6:175-82.
6. Skuta GL, Beeson CC et al. Intraoperative mitomycin-C versus postoperative 5-Fluorouracil following Glaucoma filtering surgery. Ophthalmology 1992; 99: 438-44.
7. Palmer SS. Mitomycin as adjunct chemotherapy with Trabeculectomy. Ophthalmology 1991, 98:317-21.
8. Dietze PJ, Feldman RM, Gross RL. Intraoperative application of 5-Fluorouracil during Trabeculectomy. Ophthalmic Surg. 1992; 23:662-5.
9. Larigan L, Sturmer J, Baez KA et al. Single Intraoperative applications of 5-Fluorouracil during filtering surgery early results. Br J Ophthalmol 1994 ;78:33-7.
10. Patitsas CJ, Rockwood EJ et al. Glaucoma filtering surgery with postoperative 5-Fluorouracil in patients with intraocular inflammatory disease. Ophthalmology 1992; 114:737-41.
11. Singh K, Egbert PR et al. Am J Ophthalmol 1997, 123(1);48-53.
12. Vijaya L: Mukesh BN et al. Comparison of low dose Mitomycin C vs 5-Fluorouracil in primary Glaucoma surgery: A pilot study. Ophthalmic Surg. Lasers 2000; 31(1): 24-30.
13. Smith MF, Sherwood MB et al: Results of Intraoperative 5-Fluorouracil supplementation in Trabeculectomy for open angle Glaucoma. Am J Ophthalmol 1992; 114:737-41.
14. Bell RW, Habib NE, O'Brien C. Long term results and complications after trabeculectomy with a single per operative application of 5-Fluorouracil. Eye 1997; 11:663:71
15. Vanourakin et al. Trabeculectomy with intraoperative 5-Fluorouracil or mitomycin C. Greek Annals of Ophthalmology 1998; 1:25-30.
16. Singh G, Kaur J, Dogra A. Indian J Ophthalmol 1993; 41(2): 78-80.
17. Alan Knapp, Hever DK et al. Serious corneal complications of glaucoma filtering surgery with postoperative 5-Fluorouracil. Am J Ophthalmol; 103,187:1987.
18. Huang PT. Mitomycin C in glaucoma filtering surgery. Asian J Ophthalmol vol2, no. 1,2,2000.
19. Dreyer EB, Chaturvedi N et al. Mitomycin C and 5-Fluorouracil supplemented trabeculectomies on the anterior segment. Arch Ophthalmol 1995; 113:578-80.
20. Smith MF, Doyle JW et al. Results of Intraoperative 5-Fluorouracil or lower dose MMC administration in initial Trabeculectomy Surgery. J Glaucoma 1997; 6(2): 104-110.
21. Wolner B et al. Late bleb related endophthalmitis after Trabeculectomy with