Research Article :

EFFICACY OF PREOPERATIVE SUBCONJUNCTIVAL INJECTION OF MITOMYCIN C IN TRABECULECTOMY

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Introduction:

Long-term reduction of intraocular pressure (IOP) is the mainstay of glaucoma treatment. The most common surgical method to reduce IOP remains the trabeculectomy procedure originally described by Cairns (1968)[1]. Unfortunately, a steady rate of failure has been reported after this procedure, most commonly because of scarring external to the scleral flap (Skuta & Parrish 1987)[2]. The anti-metabolite agents like 5-fluorouracil (5FU) and mitomycin C (MMC) have therefore been used to augment filtration surgery[3] . The administration of mitomycin C in glaucoma surgery is considered an off-label use by the Food and Drug Administration (FDA) because mitomycin C is classified as a group 2B carcinogen (possible for human) by the International Agency for Research on Cancer.

The method of application of anti-metabolite during trabeculectomy surgery contributes to the morphology of the drainage bleb and its long-term survival (You et al. 2002)[4]. The most preferred methord of use of MMC is to place sponges soaked with various concentrations of MMC in the subconjunctival space or below the Tenon's layer prior to scleral flap dissectionfor variable duration. (Skuta et al. 1992; Sisto et al. 2007)[3,5].Intra operative application and washing technique of MMC results in inconsistent levels of MMC available for fibroblast inhibition thus leading to either increased risk of failure or complications of excess drug like Superficial punctate corneal erosion, scleral melt and delayed conjunctival wound healing leading to leak and hypotonous maculopathy. Preoperative injection of MMC has been described by Wang et al[6] in 1992 where he performed ab interno sclerostomy by yag laser following injection of MMC with good results. Similar results were also obtained by Karp et [a71] in 1994 where abexterno sclerostomy was performed.

Ando et al(1994)[8] found that injecting subconjunctivaly 0.2 mg/ml of MMC and then subsequently washing it throughly only 3 micro gm of MMC remains in the eye. Hung et al (1995)[9] published the first human study of use of subconjunctival injection of MMC 3 to 5 days prior to Trabeculectomy and found the bleb to be avascular and diffuse and the IOP was well controlled up to 1 year . In this prospective study we selected patients of advance glaucoma who were either not controlled or who were noncompliant to medication and performed trabeculectomy after two weeks of injection of MMC below the superior bulbar conjunctiva.

Material and Methods

Subjects : Patients of uncontrolled glaucoma undergoing trabeculectomy were informed about the procedure and after consent were operated on by a single surgeon and their details prospectively entered into a computer database. This study presents the characteristics and outcomes of all those who underwent surgery with pre op subconjunctival injection MMC between August 2010 and July 2012.The results were analyzed for patients who completed one year of surgery.

Procedure : 0.1 ml of mitomycin C injection with a concentration of 0.02mg/ml(2%) was injected at the superior bulbar conjunctiva

Table 1 : Principal indication for surgery ***n* (%)**

IOP too high for disc with max medication	14 (46.2%)
Absolute / end stage glaucoma	6(30.7%)
Drug intolerance	1 (7.7%)
Not able to afford drugs	2 (15.4%)

puncturing to the subtenon space about 10 mm away from the limbus.(Fig 1) The injection site was kept pressed with a bud for 2 minutes and then the fornix was thoroughly washed with normal saline .The patient was put on antibiotic steroid combination eye drop for 2 weeks after which subjected to standard trabeculectomy procedure with limbal based flap.(Fig 2) After the sub conjunctival space was washed throughly with saline a 3X3 mm square partial thickness scleral flap was made with the trabeculectomy size of 1.5 x 1.5 mm. The scleral flap was sutured at its 2 free corners and conjunctiva was closed with purse string suture with 10 -0-nylon. Post op regimen was tapering doses of Steroid over 6 weeks, antibiotic and cyclopentolate drops for 2 weeks.

Follow Up :- All patients were seen after 1 day and 7 days post operatively and then after completion of 1, 3, 6 and 12 or more months after surgery. The IOP, medications, bleb appearance, complications and postoperative procedures were recorded in all cases in each visit.

Results :

Patients who completed at least 3 months after surgery were considered for analysis of result. 23 eyes of 20 patients which were uncontrolled with maximum medication were subjected to surgery.The patients had an average age of 69.3 (range 55 to 81 years) out of which 11(48.0%) patients were male. 12 (52 %) patients had advanced POAG , 3 had NVG and 3 had ACG, one uveitic glaucoma ,1 had Aphakic glaucoma and the rest 3 were secondary glaucomas. The average preoperative medication was 3.42.

The mean pre operative IOP was 32.39mmHg (range from 23 to 44 mmHg) which after the injection of Mytomycin C came down to 30.17 (ranging from 22 to 24 mm Hg).The mean IOP at the last follow up (at least 3 months after surgery) was 15.86mmHg (range 10 to 26 mmHg) . So the average drop in IOP after injection of MMC was 2.22mmHg and that after 3 months of surgery was 16.53mmHg. All patients completed 1 year of follow up and the average IOP was 17.1mmHg (range 14 to 25 mmHg). The mean number of medication used by the patients at 1 year was 0.43.

TABLE 2: giving the patient data, preoperative and post operative IOP.

able 3 : giving the success rates based on various criterias.

No major complication was seen post operatively. Postoperatively, one patient was noted to have bleb leak, but this was posteriorly from the site of the peritomy and no leakage from the injection site was seen in this series of patients. He required additional sutures to prevent over filtration and wound leak.(FIG 3). One patient required AC reformation with air and was put on systemic steroids to reduce the choroidal detachment . One patient had Hyphaema which resolved spontaneously .(Fig 4).Only two patients of NVG developed vascularized bleb with signs of bleb failure by 3 months.(Fig 5)**Table 3. Postoperative complications. Early (<2 weeks)** Hypotony (Less than 7 mm Hg)2(8.6%) Hyphaema1 (4.3%)Wound Leak1 (4.3%)Choroidal detachment 1(4.3%)**Late (>2 weeks)** Choroidal detachment0Vascularised/Encysted bleb2 (8.6%)

Discussion:

The aim of trabeculectomy surgery is to

TABLE 2: giving the patient data, preoperative and post operative IOP

age	sex	diagnosis	date of inj	med	pre inj iop	post inj IOP	V/A	1 week	6 weeks	1 YEAR
72	M	POAG ABSOLUTE	13-08 10	3	36	33	PL+	7	9	18
68	F	POAG	30/08/10	4	30	26	20/80	10	11	17
69	F	POAG	21/9/2010	3	32	29	20/30	15	13	16
81	F	Uveitic glaucoma	14/11/10	4	29	26	20/200	17	12	18
79	M	POAG ABSOLUTE	2/12/2010	4	33	31	PL+	14	13	15
71	F	POAG	17/02/11	4	24	26	20/100	13	11	16
64	M	chr ACG	4/3/2011	4	38	34	20/200	3	8	14
78	M	POAG	15/4/2011	3	31	28	20/40	13	12	15
75	F	NVG	23/05/11	4	36	34	PL+	15	18	17
68	M	NVG	11/6/2011	4	38	34	CF 1MT	12	19	21
80	F	POAG ABSOLUTE	19- 6-11	4	28	26	PL+	7	11	17
69	F	POAG	3/7/2011	4	27	26	20/60	11	10	16
74	M	APHAKIC	21- 08- 11	3	31	29	CF 3 MT	12	11	15
55	M	ADHERANT LEUCOMA WITH SEC GLAUCOMA	14/09/11	2	34	33	CF CF	15	16	18
62	F	ACG	23/09/11	3	29	26	20/30	18	16	15
63	F	NVG	9/10/2011	4	40	39	HM	20	22	25
59	M	FAILED PK laucoma	11/11/2011	3	33	30	CF CF	15	14	16
74	F	POAG ABSOLUTE	2/1/2012	4	44	42	PL-	18	20	18
68	F	POAG	3/3/2012	3	28	25	CF 3 MT	16	15	16
59	M	RD SX WITH SEC GLAUCOMA	17/04/12	4	36	34	CF 1MT	20	22	21
68	F	POAG	23/04/12	1	31	28	20/40	11	14	16
60	M	ACG	7/5/2012	3	34	33	CF 2 MT	9	14	15
78	M	POAG	11/6/2012	4	23	22	20/200	10	16	16

produce a long-functioning drainage fistula, with minimal risk of complications. Ideally, the bleb should be diffuse and mildly elevated, with normal vascularity (Jones et al. 2005)[10]. The area of action of MC is localized to the area of exposure (Khaw et al. 1993)[11]. Applying the anti-metabolites over a wide area is believed to reduce the risk of a cystic bleb forming as well as avoiding increased risks of premature failure caused by scarring around the drainage site (Wells et al. 2003).[12] MMC was first developed by Hata et al from Streptomyces caespitosus[13]. It interrupts cell mitosis by inhibiting cell mitosis. Intra operative use of MMC in refractory glaucoma was done by Chen et al in 1981.[14] Though the article published in 1990 by Chen et al [15] highlighted the role of MMC in preventing the inhibition of activated fibroblast around the bleb in trabeculectomy and hence the efficacy of the drug in refractory glaucoma cases recent studies have pointed the beneficial effect of MMC in primary glaucoma surgeries and even in young age group.[16] The use of MMC to modulate healing allows lower IOPs to be obtained, but it must be used cautiously to avoid thin or ischaemic blebs, which are associated with leakage and increased risks of endophthalmitis and hypotonous maculopathy. We believe that by injecting the anti-metabolite into the Tenon's layer, a diffuse area of action would be obtained and direct toxicity of the drug to the conjunctiva , cornea anterior chamber or ciliary body reduced.

Many means are used to measure

Table 3 : giving the success rates based on various criterias

Success Defination	N (%)
IOP reduction by >33% from base line	19 (82.6%)
IOP less than 21 mmHg	22 (95.6%)
IOP less than 18 mmHg	19 (82.6%)
IOP less than 15 mmHg (with out Rx)	4 (18%)

trabeculectomy success in the literature. The NTS[16], which reported the outcomes of trabeculectomy surgery in the UK in 1996, gave us a benchmark with which to evaluate our own practice. In their study 66% of patients achieved an IOP of <2/3 of listing IOP, and 84.0% achieved an IOP <21 mmHg (excluding those on anti-glaucoma medications) at 12 months. Since then, the treatment of glaucoma has evolved considerably and lower target pressures are more often chosen and achieved. We therefore used the same principal outcome .The results showed favourable IOP control was obtained in our group of patients, with low rates of complications. 95.6% of the patients undergoing Sx had an IOP 21 mmHg or less at 1 year (including those on Anti glaucoma medication) , and 82.6% were less than 18 mmHg.and achieved pressure lower than 1/ 3rd of the preoperative pressure. The reason for our lower success rate of IOP <15mmHg (18%) was mainly because of all patients were refractory glaucoma cases including many NVG. Although hypotony and hyphaema occurred in a small percentage of this cohort, these were transient problems within the first 2 weeks that were managed conservatively. This was not a comparative study, but other studies in which MMC has been applied directly to the sclera with MC-soaked sponges have reported similaror better success rates. In Beckers et al. 2003[17] study 85% achieved an IOP of 18 mmHg or less at 1 year and, Fontana et al.[18] 2006 reported 83.3% had an IOP of 15 mmHg or less at 1 year, with an IOP reduction of at least 25% .The mean pre operative IOP in both these studies were between 19 to 22 mmHg . How ever the complication rates in our series was less A concern is that the injection itself might induce fibrosis and subsequent bleb failure as subconjunctival anaesthesia was found to be associated with a lower success rate in analysis of data from the NTS (Edmunds et al. 2004)[19]. It was postulated that this finding could be caused by fibroblasts being stimulated, or alternatively that haemorrhage in the area of the injection caused premature bleb failure. The patients in our study were all given injections at the bleb site, which might therefore be thought to increase the risk of bleb failure. However, these concerns have not been reflected in our results. Injecting under the conjunctiva might risk haemorrhage, but by taking care to avoid vessels during the introduction of the needle, and by injecting fluid during advancement to displace vessels, we found that subconjunctival haemorrhage could be avoided.

Conclusion:

The technique of MMC application that we describe is more controlled and straightforward to perform. Instead of preparing and then transferring multiple fragments of a sponge material to the conjunctiva, a single injection is given to the area for treatment; this can be expected to give a uniform exposure to the area involved. Risks of retained sponge material, or inadvertent exposure of areas of conjunctiva or the corneal epithelium to MMC, are reduced. The 1-year outcome measures from this single-surgeon case series show it to be an efficacious technique with an encouraging safety profile.

Many of the complications associated with MMC occur months to years following the procedure. The long-term follow-up of our patients will therefore be studied before further conclusions regarding this technique are made. It should also be noted that this was a non-comparative study, reporting the results from a single surgeon with a specific technique. A prospective and randomized controlled trial, using a formal means of bleb assessment, would

Table 3. Postoperative complications.

Early (<2 weeks)	
Hypotony (Less than 7 mm Hg)	2(8.6%)
Hyphaema	1 (4.3%)
Wound Leak	1 (4.3%)
Choroidal detachment	1(4.3%)
Late (>2 weeks)	
Choroidal detachment	0
Vascularised/Encysted bleb	2 (8.6%)

help discern whether this technique has advantages over existing means of MMC application.

Referrence

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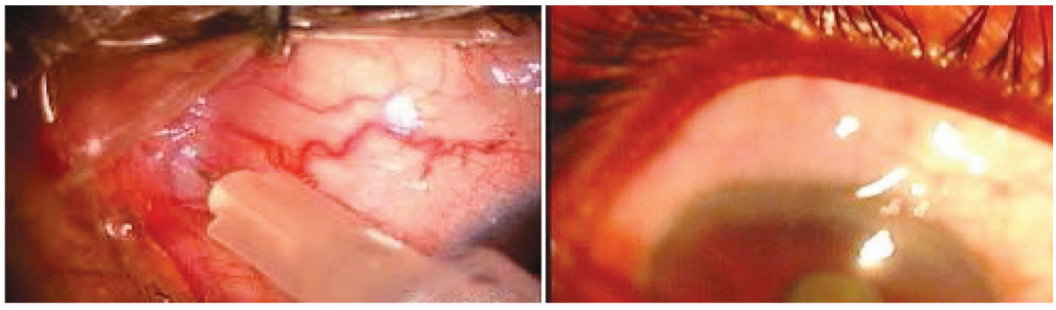

Fig 1 : Injection of MMC below th bulbar conjunctiva

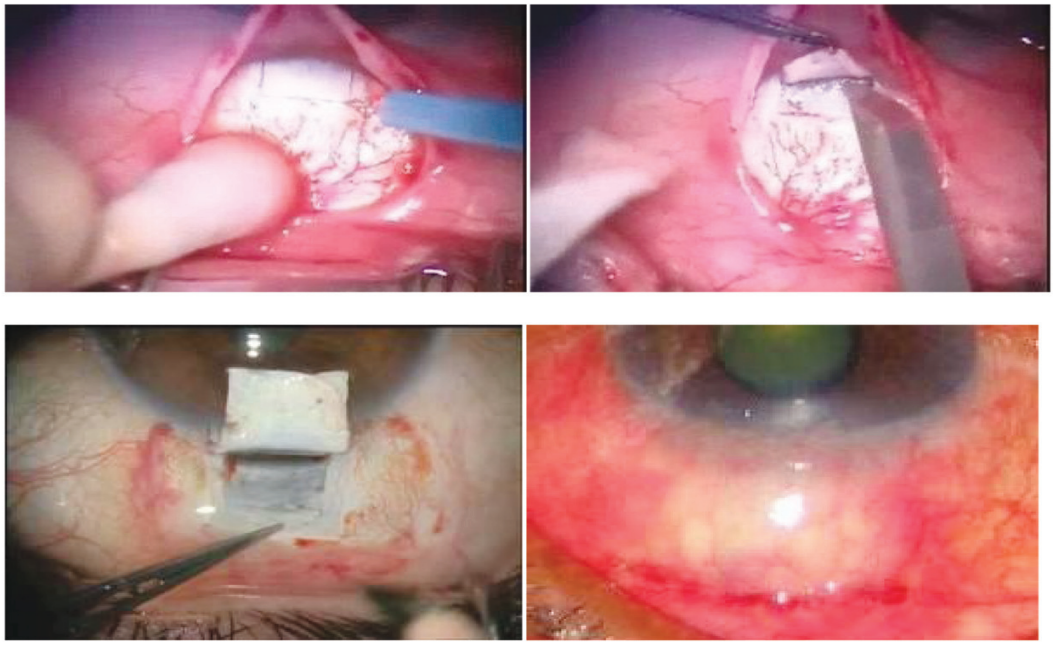

Fig 2: Standard Trabeculectomy Procedure

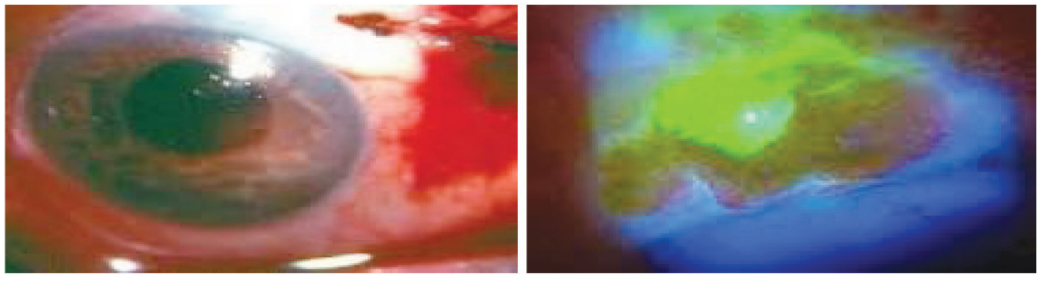

Fig 3: Hypotony with woung leak

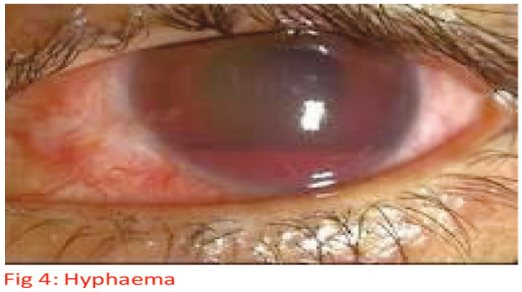

Fig 4: Hyphaema

Fig 5: Encysted Bleb