

Success and complication rates of trabeculectomies augmented with MMC in the management of glaucoma

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Abstract

Glaucoma unresponsive to medical treatment is managed by surgery. Augmentation with mitomycin C (MMC) is considered in patients at high risk of surgery failure.

Aim: In this paper we assess and compare the success and complications of this procedure performed in the local state hospital with those of larger international centres.

Methods: A retrospective study, of the surgery performed between 2003 and 2007 at St. Luke's Hospital by one surgeon (FM), was conducted. The total number of eyes considered in this analysis was 32. Intraocular pressures and complications up to one year post-operatively were recorded.

Results: The mean intraocular pressure decreased from 30mmHg pre-operatively to 18mmHg post-operatively. The mean IOP drop registered was 42%. Of the 32 eyes that underwent trabeculectomy augmented with MMC, 23 were classified as a complete success with IOP remaining below 21mmHg at 1year post-surgery. Six eyes were considered as a partial success since they had an IOP under 21mmHg but this had to be kept under control with the administration of medications. Failure of surgery was classified as uncontrollable IOP, although also on medications. This was seen in 3 eyes. Using the central limit theorem, the significance of the difference in means and difference in percentages of IOP drop and complication rates, between the local state hospital procedures and international centres, were calculated.

Conclusion: Incidences obtained from this analysis compare very favourably with results from international studies, showing no significant differences.

Keywords

Glaucoma, mitomycin C, trabeculectomy, intraocular pressure

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Glaucoma can be defined as a pathologic condition in which there is progressive loss of ganglion cell axons causing visual field damage that is related to intraocular pressure (IOP).¹ Trabeculectomy, first introduced by Cairns in 1968, is by far the most common type of glaucoma filtering surgery used in the management of glaucoma when medical treatment fails. However in high risk groups such as in young individuals, patients suffering from neovascular glaucoma, uveitic glaucoma and steroid induced glaucoma as well as in patients on previous prolonged medical treatment, there is a higher risk of scarring response at the surgical site resulting in failure of the trabeculectomy.

Therefore in such high risk glaucoma patients, modulation of wound healing would potentially increase the success rate of the trabeculectomy. Mitomycin C, an antitumour medication, inhibits DNA synthesis and thus suppresses cell proliferation. In glaucoma surgery it has been shown to inhibit fibroblast proliferation, thus preventing scarring with better surgical outcomes. These results however have been marred by complications which vary from mild, such as corneal erosions and bleb leaks, to severe, as for instance hypotonic maculopathy longstanding choroidal detachments, late bleb leaks and endophthalmitis. Recent procedures being used in the management of glaucoma include deep sclerotomy, viscocanalostomy and canaloplasty. Reports on results of these procedures have shown a low percentage of complications. However these procedures are time consuming and require significant mastering of complex new skills. In this paper we analysed the effectiveness and complications of patients who underwent trabeculectomy augmented with mitomycin and compared them to peer studies.

Method

A retrospective study was conducted in which we retrieved the records of all the patients that underwent MMC augmented trabeculectomy, between January 2003 and December 2007. This procedure was carried out on a total of 36 eyes. All operations were performed at the Eye Unit in St Luke's Hospital, Malta, by one ophthalmologist (FM). Out of the 36 interventions, 4 had incomplete pre or post-operative data and therefore they were not included in this study. All information retrieved was divided into pre-operative, intra-operative and postoperative data.

Verbal consent was obtained from the patients whose information was included in this study. No reference to any particular patient is made in this analysis.

Pre-operative

Demographic data including gender, age and race, as well as the duration and number of antiglaucoma medications every patient was on were recorded. Further information was obtained from records of the last pre-operative visit. These included the best corrected visual acuity, aetiology of glaucoma diagnosed by using biomicroscopy, intraocular pressure measurements using a Goldmann applanation tonometer and optic disc appearance using indirect ophthalmoscopy.

Operative technique

A fornix based conjunctival flap was fashioned and the sub Tenon's space dissected posteriorly alongside the length of the superior rectus. No fixation suture was used.

A partial thickness 2 X 3mm rectangular scleral flap was created. A pledget of cellulose sponge soaked in 0.04% Mitomycin C solution was then placed under the Tenon's capsule, also overlying the base of the scleral flap and left there for 2 to 2 and a half minutes. Care was taken so that the edges of the conjunctival flap were not exposed to the drug. The sponge was then removed and the space between the conjunctiva and episclera was thoroughly irrigated with saline.

The anterior chamber was subsequently entered and a sclerotomy using Kelly's punch was performed. This was followed by a guarded peripheral iridectomy. A 1.5mm paracentesis was also prepared. The scleral flap was then re-approximated with two interrupted 10-0 nylon sutures (Ethicon) with slightly greater tension than a standard trabeculectomy. At this point the paracentesis was used to verify that the anterior chamber can be maintained without a risk of overfiltration. The Tenon's capsule and conjunctiva were then sutured with two interrupted 10-0 nylon sutures to the limbus. A subconjunctival injection of

methylprednisolone acetate and ceftriaxone was administered in the inferior fornix.

Post-operative care

All patients received a standard regimen of dexamethasone and gentamicin eye drops six hourly. The antibiotic was usually stopped after 2 to 3 weeks but the steroid was tailed off over the subsequent 2 to 3 months. Topical mydriatics were only used in cases where the patient developed a shallow anterior chamber post operatively to prevent aqueous misdirection syndrome and posterior iris synechiae. Data recorded at follow-up examinations that included IOP measurements as well as any complications that developed at 1 day, 1 week, 3 weeks, 3 months, 6 months and 1 year post-operatively were available. The need for post-operative medical glaucoma treatment or the need for re-operation was also noted.

Results

Gender and causes of glaucoma

The patients operated upon were all Caucasians. The gender distribution of patients' eyes that underwent this procedure was predominantly male at 56.3% to 43.7%. The frequency in the various age groups is given in Table 1. Figure 1 shows the distribution of the causes of glaucoma operated upon.

Pre-operative IOP and antiglaucoma treatment

All the patients operated were on full anti glaucoma treatment (AGT) prior to surgery. Some patients could not be treated with the customary three IOP lowering eye drops due to hypersensitivity reactions, cardiac failure, asthma, or severe depression, the latter three being contraindications for the use of beta blockers. Others should not be treated with acetazolamide since they had allergies to sulfa drugs, significant liver and kidney disease, adrenal gland failure (Addison's disease), or developed severe side effects including lethargy, depression, confusion, toxic epidermal necrolysis, photosensitivity reactions, urticaria, thrombotic thrombocytopenic purpura, nausea, vomiting and hypokalaemia.

The patients operated upon were on the pre-operative antiglaucoma treatment shown in Figure 2.

Figure 3 shows the distribution of pre-op IOP with the mean pre-operative IOP being 30mmHg.

Figure 1: Causes of glaucoma for which operations were performed

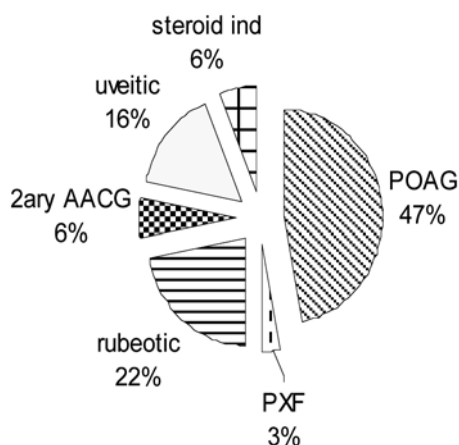


Table 1: Frequency of operated patients according to different age groups

Age groups	Number of patients
10-20	2
21-30	0
31-40	3
41-50	6
51-60	8
61-70	6
71-80	7

Outcome of surgery

Early post-operative IOP and IOP one year post-op are shown in Figure 4 and 5 respectively.

The mean post-operative IOP one year after surgery stabilized at 18mmHg. There was a drop in IOP in 29 of the 32 eyes operated upon.

Figure 6 depicts the percentage IOP drop in the 29 eyes that registered a drop in IOP post-op. The mean IOP drop registered was 42%.

The surgeries performed were considered a complete success if the IOP was stabilized below 21mmHg and no deterioration in visual fields and optic nerve appearance was recorded. There were no patients with a post-operative IOP of less than 21mmHg that recorded deterioration in visual fields or further optic nerve damage. Partial success surgery was considered as having an IOP under 21mmHg (together with stable visual fields results and optic nerve appearance) kept under control with the administration of medications. Failure of surgery was classified as uncontrollable IOP, although also on medications, together with progressive nerve damage and glaucomatous visual field defects. Hypotony was defined as IOP of less than 8mmHg documented at 2 early post-operative visits. Table 2 summarises the results obtained.

Complications

The main complication associated with the use of MMC in trabeculectomy is the development of cystic thin-walled blebs that predispose to chronic hypotony, late-onset bleb leak and endophthalmitis.

Nine of the eyes operated upon had an excessive drop in IOP. Of these, eight suffered from early hypotonicity and the other suffered from late hypotonicity. Three of the eyes got hypotonic maculopathy due to an excessively low IOP. Two patients underwent further surgery since the IOP failed to stabilise. In both these patients autologous blood injection and subsequent refashioning of the bleb had to be carried out, both with good end IOP control.

The desired reduction in IOP failed for three eyes. All these patients were rubeotic glaucoma patients. One had pre-op bullous keratopathy and the aim of the operation in this case was to decrease the IOP to gain some pain relief. An increase in IOP by 14% was registered. Another patient developed a

severe hyphaema and as a result, the IOP post-op remained the same as the pre-op IOP. The third patient underwent repeat trabeculectomy augmented with MMC and the IOP went down by 40.7% after this second operation.

A break down of the complication rates (Figure 7) shows that early hypotonicity is predominant, followed by hyphaema. No cases of blebitis or endophthalmitis were reported, however a lifetime risk of blebitis remains especially for those patients with cystic blebs.

It is worth noting that three of the thirty two eyes had undergone surgical trabeculectomy before trabeculectomy augmented with MMC was carried out. In the early post-op phase, thirteen had to perform regular ocular massage for proper filtration and bleb formation and eight eyes underwent laser suture lysis for control of IOP. Worst IOP control and highest complication rates occurred in rubeotic eyes.

The operations carried out in which the IOP failed to decrease sufficiently even after administering medical treatment were all for rubeotic glaucoma. One achieved a good decrease in IOP but the final IOP was still high at more than 21mmHg. The other patient had pre-op decompensating bullous keratopathy.

Comparison of results

The above results were compared with other studies carried out in specialized centres and the significance of the difference in means and of the difference in proportions, depending on the information available from the other studies, was calculated. (Table 3).

Table 2: Surgery success rates

Complete success	IOP <=21mmHg	23 eyes
Partial success: controlled	On 1 AGT drops	3 eyes
	On 2 AGT drops	1 eye
	On 3 AGT drops	1 eye
	On 3 AGT drops + acetazolamide PO	1 eye
Failure	On full AGT and still not controlled	3 eyes

Figure 2: Pre-operative anti-glaucoma treatment

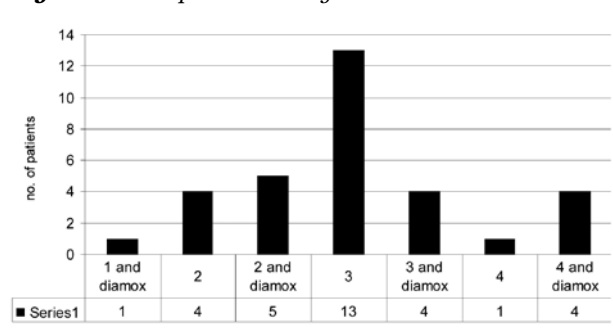
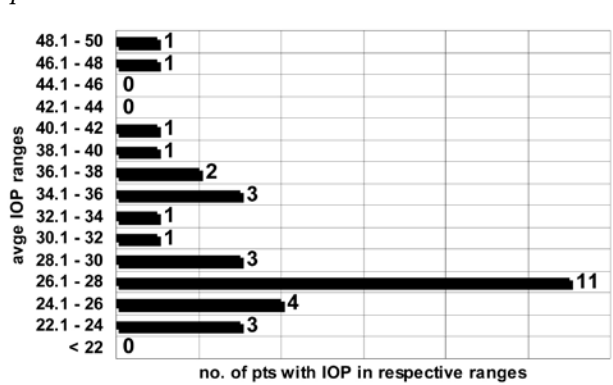


Figure 3: Distribution of pre-operative intra-ocular pressure



The significance of difference in means

Using the Central Limit Theorem, the *t*-statistic,

$$t = \frac{(x_1 - x_2)}{\sqrt{\text{var} \left(\frac{1}{n_1} + \frac{1}{n_2} \right)}}$$

approaches the 0+/-1 normal distribution with variance,

$$\text{var} = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2},$$

where the variance (var) is the square of the standard deviation,

- n_1 = no. of patients in this study,
- n_2 = no. of patients in the study being compared to,
- x_1 = mean of the values of this study
- x_2 = mean of the values of the study being compared to

The mean IOP drop obtained in the eyes operated by Mercieca were compared to that of those reported in the study by Zacharia *et al.*² On the other hand, the mean IOP post-op was compared to that of the study carried out by Casson *et al.*³ Table 4 demonstrates the results obtained. It is important to note that the cohort of patients used in the study carried out by Zacharia, included black patients whose glaucoma is more difficult to control than that of caucasians.

In both cases, the *t*-analysis value is less than the standard values at the 5% level of significance. Thus we conclude that the difference in means between Mercieca's and the respective studies is not significant.

Significance of difference in proportions

The formulae for the distribution of proportions used are:

$$z = \frac{(m_1 - m_2)}{\sqrt{\rho(1 - \rho) \left(\frac{1}{n_1} + \frac{1}{n_2} \right)}} \quad \text{and} \quad \rho = \frac{(m_1 n_1 + m_2 n_2)}{100(n_1 + n_2)}$$

where

- = no. of patients in this study
- = no. of patients in the study being compared to
- = mean of the values of this study
- = mean of the values of the study being compared to
- ρ = pooled proportion

The proportion of eyes that developed hypotonicity in this study were compared to those in the studies carried out by Hyung *et al.*⁴ and Zacharia *et al.*² The incidence of development of maculopathy reported by Hyung *et al.* was also compared to that reported in our patients. We also compared the results of surgery that was classified as a complete success with those reported by Megevand *et al.*⁵ The *z* value of this analysis and the *z* value provided from standard calculated tables depending on the degrees of freedom at the 5% level of significance are displayed in table 5.

These results show that the difference in proportions between results obtained in Mercieca's patients and the respective studies is not significant.

Discussion

Compounds that modulate wound healing post-trabeculectomy have been investigated in the hope of obtaining an increase in the success of glaucoma filtering

Table 3: Comparison of local results to published data

	Compared study	Local study	Total no. of eyes of compared study	Total no. of eyes of local study
Mean IOP drop	Zacharia: 12.3 mmHg	12.88mmHg	52	29*
Mean IOP post-op	Casson: 14 mmHg	18mmHg	21	32
Hypotonicity	Hyung: 30 eyes	8 eyes	117	32
Hypotonicity	Zacharia: 17 eyes	8 eyes	52	32
Maculopathy	Hyung: 11 eyes	3 eyes	117	32
IOP <21mmHg	Megevand: 22 eyes (in the 2min exposure to MMC group)	23 eyes	25	32

* There was a drop in IOP in 29 of the 32 eyes operated upon. Only these were considered in the calculation of the mean IOP drop

Table 4: Comparison of local results to published data

Compared studies	t (audit) 5% significant	t table	Degrees of freedom
Mercieca : Zacharia Mean IOP drop	0.248	2.047	28
Mercieca : Casson Mean IOP postop	0.259	2.04	31

Figure 4: Early post-op IOP

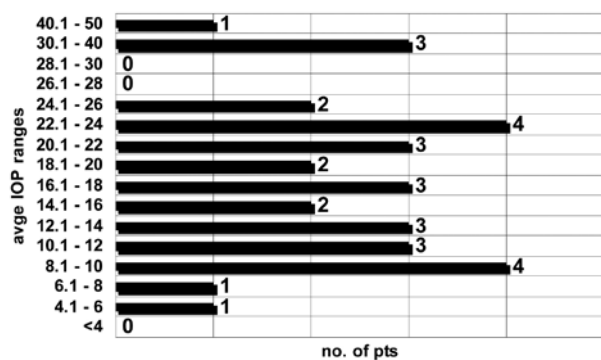


Figure 5: IOP one year post-op

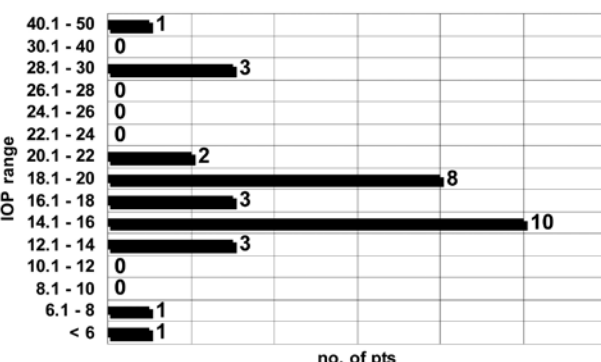


Figure 6: Percentage post-op intra-ocular pressure drop

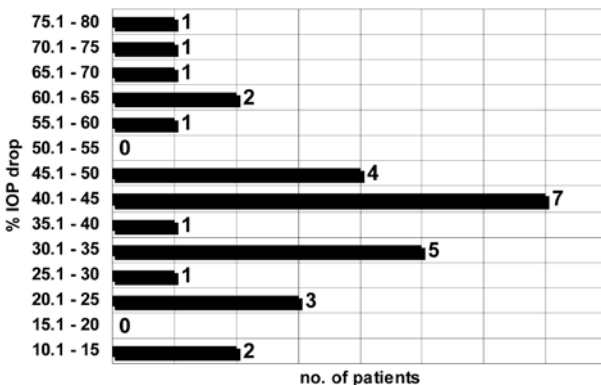
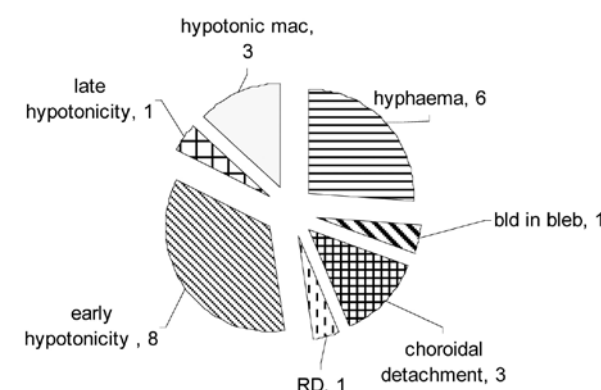


Figure 7: Complications occurring post-op



surgery.⁶ 5-Fluorouracil was the first antimetabolite drug used in trabeculectomy to prevent scarring of the filtration bleb after glaucoma filtering surgery.⁷ Its use requires intraoperative application followed by a variable number of postoperative subconjunctival injections of 5 Fluorouracil in the trabeculectomy area. Consequent complications such as corneal epithelial defects, corneal opacification and conjunctival wound leaks discouraged its widespread use.^{26,27} In 1983, Chen⁸ reported that complications occurring with the use of 5-fluorouracil, *were encountered less frequently with MMC*. Since then MMC has been primarily considered in the context of known risk factors for failure of trabeculectomy.^{22-25,28,29} Among the higher risk factors for surgery failure we find neovascular glaucoma, a previously failed trabeculectomy, and certain secondary glaucomas (e.g. inflammatory, post-traumatic angle recession and iridocorneal endothelial syndrome). Intermediate risk factors include the use of topical antiglaucoma medication for over 3 years, previous conjunctival surgery and previous cataract surgery.^{7,9-15}

Palmer¹⁶ carried out a study which confirms that MMC as adjunct chemotherapy with trabeculectomy is effective in delaying progression of cupping or visual field loss. This was confirmed further by Hagiwara et al¹⁷ in 2000.

Most of the complications observed in this study seemed to be secondary to excessive filtration. 8 of the 32 eyes suffered from early hypotonicity and 1 suffered from late hypotonicity. 3 eyes developed hypotonic maculopathy and 3 suffered from choroidals. None of the choroidal effusions that developed in our patients required surgical drainage. It is thought that hypotony leads to inward movement of the scleral wall, resulting in chorioretinal wrinkling, disc swelling and vascular tortuosity.¹⁸ The chorioretinal folds in the macular area and RPE changes seen in a later stage of the process are responsible for the visual acuity loss.¹⁹ Other clinical features include thickening of the cornea associated with striae at Descemet's membrane, shallow anterior chamber, peripheral anterior synechiae, suprachoroidal haemorrhage and choroidal detachment. Both overfiltration because of tissue disorganization of the filtering bleb and aqueous hyposecretion because of ciliary body toxicity might be involved in the causes of persistent hypotony after using MMC.

Zacharia *et al*² investigated the incidence of hypotony after trabeculectomy with MMC. Hypotony occurred in one third of these eyes. They proved that there is a statistically significant association of hypotony with longer application time of mitomycin C. Subsequent retrospective comparative studies carried out by Mégevand, Salmon *et al*⁵ found that a 2-minute application of 0.2 mg/ml MMC is as effective as a 5-minute exposure with the complication rate remaining unaltered. The optimum dose for a balance between utilizing the antimetabolite properties of MMC and preventing its serious complications is still under research.

In 2003, Hyung and Jung⁴ studied the management of hypotony after trabeculectomy with MMC. The following

Table 5: Comparison of local results to published data

Compared studies	z (audit)	z table: 5% significance	Degrees of freedom
Mercieca : Hyung Hypotonicity	-0.0737	1.960	147
Mercieca : Zacharia Hypotonicity	-0.7488	1.920	82
Mercieca : Hyung Maculopathy	-0.0045	1.960	147
Mercieca : Megevand IOP<21	-1.4800	2.005	55

methods in a stepwise manner were applied: medical treatment, intrableb autologous blood injection, additional sutures to the scleral flap, necrotic bleb excision and advancement of the forniceal conjunctival flap. They also concluded that the most prevalent risk factors of hypotony were young age and primary open angle glaucoma. Thus one has to be cautious in the use of MMC for juvenile primary open angle glaucoma.²⁰ Studying further patient variables that determine the fibrotic response and the susceptibility to hypotonous maculopathy would certainly help in the treatment of these challenging cases.

Limitations of data collection

Limitations of this study were mainly due to the retrospective nature of the analysis which limited us in the amount of information that was available. Data of four operations could not be retrieved. In two of the cases, not enough pre-operative or post-operative information was available since one patient was operated urgently with little pre-op information while the other was lost to follow up. In the other two cases, access to the data was not possible; one patient passed away, while, the other patient, was admitted in another hospital at the time the study was being carried out. Also, all the patients operated upon were all Caucasians. As such, the results of our study may not apply to patients from other ethnic backgrounds.

Conclusion

The overall goal for all glaucoma treatment is to preserve useful vision. Glaucoma is a multifactorial disease but the intraocular pressure is still the only known treatable risk factor. Substantial pressure reduction is difficult to achieve without filtering surgery. Antiproliferatives have increased the odds of retaining the pressure reduction after filtering surgery, and as a result they have decreased the progression of visual field defects and optic nerve damage. In this analysis, 23 out of the 32 eyes operated upon were a complete success while 6 of the operated eyes were a partial success. With regards to complication rates, early hypotonicity is predominant, followed by hyphaema. Incidences obtained from this analysis compare very favourably with results from international studies. In fact, there were no significant differences in the trends and percentages regarding complications, IOP drop and control between results from our data and those from international studies.

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