Comparison of the Success Rate of Trabeculectomy with OculusGen versus Trabeculectomy with Mitomycin C

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Abstract

***Purpose*:** To compare the effectiveness and safety of trabeculectomy with mitomycin C (MMC) versus trabeculectomy with OculusGen

***Methods*:** In this prospective study 14 eyes of 7 patients with a diagnosis of primary open angle glaucoma (POAG) that required trabeculectomy for both eyes were enrolled. For each patient we randomly performed trabeculectomy with MMC for one eye and trabeculectomy with subconjunctival OculusGen for fellow eye. Main outcome measures were: intraocular pressure (IOP), number of IOP reducing medications and surgical complications. Data analysis was performed using SPSS software version 15.

***Results*:** Mean age of the patients was 59±12.6 years. Mean duration of follow-up was 13±3.7 months for OculusGen group and 14.42±6.6 months for MMC group. Mean preoperative IOP was 19.14±3.8 mmHg with 3.14±0.37 number of medication and at last visit was 14.43±3.3 mmHg with 0.86±1.21 number of medication for OculusGen group. Mean preoperative IOP was 21.71±4.1 mmHg with 2.86±0.89 number of medication and at last visit was 12.29±3.5 mmHg with no medication for MMC group. The cumulative success at last visit was 100% in MMC group and 71.5% in OculusGen group (P=0.008%). No systemic or ocular complications related to MMC or OculusGen were seen.

***Conclusion*:** Trabeculectomy with OculusGen is a safe procedure with IOP reduction, at least in short-term, comparable to trabeculectomy with MMC, but with significantly more requirements for IOP lowering medications.

***Keywords*:** Glaucoma, Trabeculectomy, OculusGen, Mitomycin C

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Introduction

Glaucoma is the second leading cause of blindness in the world.[1] It is generally thought that vision is preserved in glaucomatous eyes when eye pressure is kept at a lower level than that at which damage to the optic nerve has occurred.[2] Glaucoma is usually treated with medical therapy but in certain situations like poor compliance of the patient and disease progression, surgical intervention becomes the first choice of treatment. Glaucoma filtration surgery lowers intraocular pressure (IOP) by creating an opening between the anterior chamber and the subconjunctival space for the drainage of aqueous humor. Trabeculectomy has been used for more than 40 years and still is the most common incisional surgery for glaucoma.[3] There are many factors which can adversely affect the outcome of trabeculectomy including: history of previous incisional surgery involving the superior conjunctiva,[4,5] prolonged use of topical anti-glaucoma medication,[6,7] black race,[8,9] and young ages (<50 years).[10,11] Other factors are associated with increased risk of failure after glaucoma filtration surgery like, aphakia,[12,13] uveitis,[14,15] rubeosis iridis,[16,17] angle recession[18] and angle closure glaucoma.[19,20] Filtration surgery also has been reported to have a lower success rate in Asian than Caucasian populations.[21,22] The main cause of failure in trabeculectomy is postoperative subconjunctival scarring at the site of surgery, which is mainly mediated by fibroblast proliferation, migration and contraction. Conjunctival scarring that consisting of linear collagen deposition can cause blockage of aqueous outflow by creating adhesions between conjunctiva and episclera, and between scleral flap and underlying tissues.[23,2] Since 1980's anti-scarring anti-metabolites such as 5-fluorouracil (5-FU) and mitomycin C (MMC) are widely used to augment the success of trabeculectomy.[24] Both MMC and 5-FU reduce fibroblast proliferation in the subconjunctival space as well as in the tenon capsule.[25,26] However, these agents can cause adverse effects such as hypotony with maculopathy, cystic thin avascular bleb, bleb infection, endophthalmitis[27-30] and late-onset leaks (>3 months after surgery).[31]

The biodegradable collagen matrix implant (≥90%collagen, ≤10%glycosaminoglycan), marketed initially as OculusGen™ (OculusGen biomedical Inc. Taipei, Taiwan) and currently as Ologen™ and iGen™, is a novel bioengineered implant designed to be used at the time of trabeculectomy. It consists of a collagen-based scaffold containing thousands of microscopic pores. The implant is placed directly over the scleral flap and influences the healing process by forcing fibroblasts and myofibroblasts to grow into the pores and secrete connective tissue in the form of a loose matrix. Theoretically this implant can decrease scar formation and improves surgical success over trabeculectomy performed without the adjunctive use of anti-fibrotic agents. Preliminary study has demonstrated that the biodegradable collagen matrix is effective for use in trabeculectomy; although it may be associated with an increased risk of early postoperative hypotony.[32] The purpose of this study was to compare the outcomes of trabeculectomy with OculusGen implant and trabeculectomy with MMC in patients requiring glaucoma surgery in both eyes.

Methods

In this prospective, randomized, interventional case series, 14 eyes of 7 patients with diagnosis of primary open angle that was not controlled and/or tolerated the medication and required trabeculectomy for both eyes were enrolled. Exclusion criteria were history of prior ocular surgery, pregnancy or breast feeding, age<30 years, normal tension glaucoma and history of ocular surface infection in recent two weeks. Signed informed consent was obtained from all patients and the ethics committee of the university approved the study. For each patient we randomly, by flipping a coin, performed trabeculectomy with MMC for one eye and trabeculectomy with OculusGen (Implant: Thickness 4mm±0.3mm, Diameter 7.0±0.5 mm) for the other eye. Trabeculectomy with fornix-based conjunctival flap and trapezoidal 3×2 mm scleral flap at supranasal quadrant was performed under general anesthesia. For eyes in OculusGen group, after sclerectomy by Kelly punch and peripheral iridectomy, scleral flap was closed by one loose 10-0 nylon suture at the center

of the flap and then OculusGen was placed on top of the flap. For eyes in MMC group, after preparing scleral flap, MMC (0.2 mg/ml) was applied by multiple thin sponges under the conjunctiva and scleral flap for 3 minutes. The area was then irrigated thoroughly with 50 cc balanced salt solution. Then sclerectomy and peripheral iridectomy was performed and scleral flap was closed by two 10-0 nylon suture with releasable technique. At the end of surgery conjunctiva was closed by 10-0 nylon sutures. All patients were treated with chloramphenicol eye drop, 4 times a day for 2 weeks and betamethasone eye drop every 2 hours for two weeks that was tapered off slowly in 6-8 weeks. Each study participant underwent a comprehensive ophthalmic evaluation, including best corrected visual acuity (BCVA) testing, IOP measurement with a calibrated Goldmann applanation tonometer, slit-lamp biomicroscopy, visual field testing (24-2 Humphrey visual field), gonioscopy and funduscopy before operation. At each postoperative visits all the examinations, except visual field testing and gonoiscopy were performed. Mean of the 3 IOP measurements taken in each eye at each visit represented the IOP for that eye. Table 1 shows patient characteristics in both groups.

There were 7 postoperative follow-up visits within 6 months after surgery for all patients: days 1, 7, 14, 30, 60, 90 and 180. A window of ±10 days was allowed for the 30, 60, 90 day visits and one of ±14 days was allowed for the 180 day visit. After 6 months, follow-up visits were continued every 2-3 months. The second eye was operated 1-6 months after the first eye. At the end of study, data analysis was performed using SPSS software version 15. Differences between preoperative and postoperative IOP and medication were compared by Mann–Whitney U test. P values of <0.05 were considered statistically significant.

Complete success was defined as an IOP ≤21 mmHg without anti-glaucoma medication and at least 20% reduction of pre operative IOP.

Table 1. Patients characteristics in Trabeculectomy with OculusGen and Trabeculectomy with mitomycin C group (n =7)

Characteristics	OculusGen	Mitomycin C	P
Age (years)			
Mean±SD	59±12.6	59±12.6	
Range	43-76	43-76	
Gender			
Male	4	4	
Female	3	3	
Laterality			
Right eye	4	3	
Left eye	3	4	
Preoperative IOP (mmHg)			
Mean±SD	19.14±3.8	21.71±4.1	0.25
Range	12-23	18-30	
No. of preoperative medications			
Mean±SD	3.14±0.37	2.86±0.89	
Range	3-4	1-4	0.46
Glaucoma type			
Primary open angle (No. eyes)	7	7	

IOP: Intraocular pressure
No: Number
SD: Standard deviation

Qualified success was defined as each of the following:

1- IOP≤21 mmHg with anti-glaucoma medication
2- IOP>21 mmHg but reduction of at least 30% from baseline with or without anti-glaucoma medication (maximum number of IOP lowering medication should not be more than preoperative)
3- In patients with IOP≤21 mmHg before operation, if the last postoperative IOP was any how lower than or equal to pre operative IOP and at least reduction of 2 IOP lowering drugs.

Cumulative success was the sum of Qualified and Complete success.

Failure of treatment was defined as one of these criteria: IOP less than 5 mmHg, IOP higher than 21 mmHg but with reduction of less than 30% from baseline with anti-glaucoma medication, requirement for reoperation according to defined target pressure and cases which not respect our definitions for success.

Results

Fourteen eyes of 7 patients (4 males and 3 females) with mean age of 59±12.6 years (range, 43-76 years) were enrolled. For each patient we performed trabeculectomy with MMC for one eye and trabeculectomy with OculusGen for the fellow eye. Mean duration of follow-up was 13 months (range, 6-18 months) for OculusGen group and 14.42±6.6 months (range, 6-23 months) for MMC group.

Mean preoperative BCVA was 0.87±1.1 (range, 0-3) logMAR for OculusGen group and 0.91±1.8 (range, 0-3) logMAR for MMC group. Mean postoperative BCVA at month 6 was 1.1±1.45 (range, 0-4) and at last visit was 1.04±1.45 (range, 0-4) for OculusGen group and mean postoperative BCVA at month 6 was 0.5±0.63 (range, 0-1.8) and at last visit was 0.51±0.62 (range, 0-1.8) for MMC group. Mean preoperative IOP was 19.14±3.8 mmHg (range, 12-23 mmHg) with 3.14±0.37 number of IOP lowering medications (range, 3-4) and mean postoperative IOP was 9.86±4.1 mmHg (range, 5-18) on day 1, 12.43±6.3 mmHg (range, 4-22) on day 7, 14.29±4.9 mmHg (range, 10-22) at month 1, 16.14±5.7 mmHg (range, 10-28) at month 3, 13.86±3.3 mmHg (range, 10-19) at month 6 and 14.43±3.3 mmHg (range, 10-19) at last visit for OculusGen group. Table 2, shows the preoperative and postoperative characteristics in OculusGen group.

Mean preoperative IOP was 21.71±4.1 mmHg (range, 18-30 mmHg) with 2.86±0.89 number of IOP lowering medications (range, 1-4) and mean postoperative IOP was 9.57±5.3 mmHg (range, 3-20) on day 1, 8±3.6 mmHg (range, 4-14) on day 7, 9.43±3.4 mmHg (range, 5-15) at month 1, 11.14±3.5 mmHg (range, 5-15) at month 3, 11±2.8 mmHg (range, 7-15) at month 6 and 12.29±3.5 mmHg (range, 8-18) at last visit for MMC group.

Table 3 shows the preoperative and postoperative characteristics in MMC group. Figure 1 shows preoperative and postoperative mean IOP in each group.

There was no statistically significant difference in postoperative IOP between the two groups at month 6 after surgery and at last visit respectively (P=0.11 and P=0.26). Mean IOP reduction at the end of month 6 and at last visit were 5.28 mmHg (range, 0-13) and 4.71 (range, 0-13) for OculusGen group and were 10.71 mmHg (range, 4-20) and 9.42 (range, 0-20) for MMC group respectively. The amount of IOP reduction between the two groups was not statistically significant, neither at month 6 after surgery (P=0.054) nor at last visit (P=0.223).

Mean IOP lowering medications at the end of month 6 and at the last visit were 0.71 (range, 0-3) (P=0.004) and 0.86 (range, 0-3) (P=0.005) for OculusGen group (only one patient needed 3 medications for achieving target IOP) and 0.00 (P=0.001) and 0.00 (P=0.001) for MMC group respectively. Four out of seven eyes in OculusGen group and all eyes in MMC group were off medication at the last visit (P=0.04).

Based on our definitions for success, at month 6 complete success was 57% (4 from 7 cases), qualified success was 14% (1 from 7 cases) and cumulative success was 71.5% (5 from 7 cases) and at the last visit complete success was 43% (3 from 7 cases), qualified success was 28.5% (2 from 7 cases) and cumulative success was 71.5 (5 from 7 cases), in OculusGen group.

At month 6 complete success was 100% (7 from 7 cases) and at last visit, complete success was 71.5% (5 from 7 cases), qualified success was 28.5% (2 from 7 cases) and cumulative success was 100% (7 from 7 cases) in MMC group. At the end of month 6, the cumulative success in MMC group was significantly better than OculusGen group (P=0.008) and 43% of cases in OculusGen group required IOP lowering medications. In both groups, those cases with the definition of qualified success had IOP less than 21 mmHg before surgery, but during the postoperative period, although at least two IOP lowering medications were reduced, the defined 20% reduction of IOP was not achieved.

The amount of reduction in anti-glaucoma medication between the two groups was not statistically significant, neither at month 6 after surgery (P=0.601) nor at the last visit (P=0.395). Table 4 shows the preoperative and postoperative characteristics between the groups.

None of the patients experienced systemic or ocular complications (significant intraocular inflammation, postoperative hyphema, endophthalmitis, flat AC, choroidal hemorrhage, persistent corneal edema and bleb-related complications) which needed any specific surgical or medical interventions.

Table 2. Comparison of preoperative and postoperative characteristics in OculusGen group

Characteristics	Preoperative	Postoperative (month 6)	Postoperative (last follow-up)
Best corrected visual acuity (logMAR)			
Mean	0.87±1.1	1.1±1.45 (P=0.203)	1.04±1.45 (P=0.360)
Range	0-3	0-4	0-4
IOP (mmHg)			
Mean	19.14±3.8	13.86±3.3 (P=0.024)	14.43±3.3 (P=0.043)
Range	12-23	10-19	10-19
Number of IOP lowering medications			
Mean	3.14±0.37	0.71±1.2 (P=0.004)	0.86±1.2 (P=0.005)
Range	3-4	0-3	0-3

IOP: Intraocular pressure
logMAR: Logarithm minimum angle of resolution
P value: Between preoperative and postoperative values

Table 3. Comparison of preoperative and postoperative characteristics in mitomycin C group

Characteristics	Preoperative	Postoperative (month 6)	Postoperative (last follow-up)
Best corrected visual acuity (logMAR)			
Mean	0.91±1.8	0.5±0.63 (P=0.081)	0.51±0.62 (P=0.094)
Range	0-3	0-1.8	0-1.8
IOP (mmHg)			
Mean	21.71±4.1mmHg	11.0±2.8 mmHg (P=0.001)	12.29±3.5 (P=0.009)
Range	18-30	7-15	8-18
Number of IOP lowering medications			
Mean	2.86±0.89	0 (P=0.001)	0 (P=0.001)
Range	1-4	0	0

IOP: Intraocular pressure
logMAR: Logarithm minimum angle of resolution
P value: Between preoperative and postoperative values

Table 4. Comparison of preoperative and postoperative characteristics between the two groups

Characteristics	OculusGen	Mitomycin C	P
Preoperative IOP	19.14±3.82	21.71± 4.1	0.25
IOP at month 6	13.86±3.3	11.0±2.8	0.11
IOP at last visit	14.33±3.3	12.29±3.5	0.26
NO. of IOP lowering medications at month 6	0.71±1.25	0.0	0.002
NO. of IOP lowering medications at last visit	0.86±1.21	0.0	0.002

IOP: Intraocular pressure
NO: Number

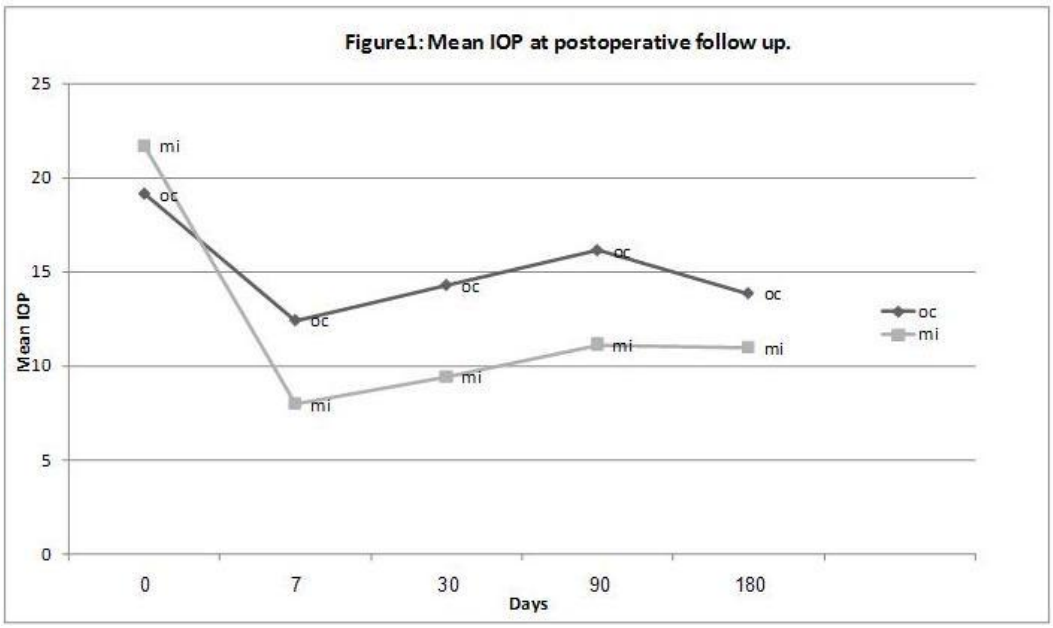

Figure 1. Mean intraocular pressure (mmHg) at baseline and during the 6 month follow-up in mitomycin C and OculusGen group.

Discussion

Trabeculectomy first introduced by Cairns[33] in 1967 and later modified by Watson in 1970.[34] Since that time it has been the commonly accepted method of surgical treatment for various types of glaucoma. Trabeculectomy involves creating a drainage channel to redirect the flow of aqueous out of the eye. According to different studies, reported success rate of trabeculectomy without anti-fibrotic agents and with follow-up of 3 months to 5 years had been from 68% to 95.4%.[35-38] The wound healing response is the most important determinant of the final IOP after trabeculectomy, with excessive postoperative scarring which significantly reducing the success rate.[23,2]

Adjunctive anti-metabolites, such as 5-FU and MMC, are commonly used to enhance success after trabeculectomy.[39,40] There are evidences that these agents increase success rates after primary and repeat trabeculectomy. The first report of glaucoma surgery with adjunctive MMC was by Chen in 1983.[41] The benefits of MMC and 5-FU have been demonstrated in several clinical trials.[41-45] Some studies show that success rate of trabeculectomy with MMC with 3 months to 3 years follow-up is from 62% to 93%.[46-48] The success rate of trabeculectomy with 5-FU in studies with 10 months to 3 years follow-up has been reported from 61% to 93.9%.[49-51] However the use of 5-FU and MMC is not

without risks. Potential risks include formation of thin avascular bleb and compromised conjunctival surface defense mechanisms predisposing the eye to infection. Other complications include over-filtration leading to hypotony with maculopathy and reduction of vision. 5-FU is also associated with corneal epithelial toxicity leading to tearing, discomfort and blurred vision.[52] MMC also has its own complications such as ciliary body damage (resulting in hypotony), corneal endothelial cell damage, limbal stem cell deficiency[53,55] hyphema, choroidal detachment[56,57] and severe uveitis.[55] These complications lead to the continued research for alternative intraoperative anti-scarring treatment. One of these modalities which has been introduced during the past few years is OculusGen (recently called ologen). This is a biodegradable collagen glycosaminoglycan matrix (biodegradable within 30-90 days) which occupies subconjunctival space by its volume and guide randomly the fibroblast growth inside the matrix.[58] There are a few and mostly unpublished studies regarding this material.

Gunenc et al found that trabeculectomy, viscocanalostomy and phacoviscocanalostomy with OculusGen implant lowers IOP effectively and safely in short term (1-12 months) follow-up. (U Gunenc, G Arikan, G Cingil, trabeculectomy and viscocanalostomy with OculusGen implant: short-term results, Dokuz Eylul University School of Medicine, Izmir, Turkey, poster presented at the world glaucoma congress; July 18-21, 2007; Singapore).

Chen et al in a multi-center, prospective and nonrandomized study, found 58.3% reduction in mean intra ocular pressure after 9 months follow-up in 59 eyes with refractory glaucoma that had undergone trabeculectomy with OculusGen implantation. The mean preoperative IOP was 38.7±7.5 mmHg with 2.1±0.9 anti-glaucoma medications and postoperatively, the mean IOP at last follow-up was 16.1±3.2 mmHg with 0.3±0.2 anti-glaucoma medications. There was no reportable complication [Chen HSL, Hsu WC. Clinical experience with biodegradable 3 D porous collagen glycosaminoglycan scaffold (OculusGen) for treatment of refractory glaucoma. Poster presented at the: Southeast Asian Glaucoma Interest Group; December 1, 2006; Chennai, India].

Dimitris Papaconstantinou et al compared the outcomes of trabeculectomy with or without ologen implant in patients requiring glaucoma surgery. 5-FU as adjuvant therapy (5 mg) was injected twice weekly in both groups, in cases with postoperative encapsulated blebs. Six months after surgery, 18 (90%) study eyes and 18 (90%) control eyes were considered complete successes. All eyes in the study group and 95% of the eyes in the control group were considered qualified successes. They showed that trabeculectomy with ologen does not seem to offer any significant advantages compared with trabeculectomy alone.[59]

Rosentreter et al compared the trabeculectomy with MMC (10 patients) and trabeculectomy with ologen (10 patients), absolute success at the end of year 1 was 100% in MMC group and 50% in ologen group, with more avasular bleb in MMC.[60]

The tendency for scar formation at the site of surgery which is the main cause of failure in trabeculectomy is related to many known and unknown individual characteristics. So in each eligible patient for surgery, comparing the results of surgery when enrolling one eye to MMC and the others to OculusGen can be more helpful and reliable. Based on this concept, in our study we randomly assigned one eye in each patient to MMC and the other eye to OculusGen. Cumulative success rate in OculusGen group was 71.5% and in MMC group was 100% (P=0.008), also 43% of cases in OculusGen group needed some medications for controlling the IOP. Differences of preoperative and postoperative IOP at month 6 and at last visit were statistically significant in both groups.

The mean reduction of IOP, 6 months after surgery in OculusGen group was 5.2 mmHg compared to the 10.7 in the MMC group, although it was not statistically significant (P=0.59), but from the clinical point of view specially based on the early manifest glaucoma trial study (EMGT) that showed each 1 mmHg decrease in IOP reduces the chance of glaucoma progression by 10%, can be considered favoarable.[61]

Therefore in patients with advanced glaucoma who needed a lower IOP, still trabeculectomy with MMC seems to be a

better choice. Regarding the intraoperative and postoperative complications, we didn't find any adverse effects related to MMC or OculusGen. In this study, because of the lack of the imaging devices with the ability to take a good quality images, we couldn't compare the morphologic features of the bleb based on the accepted international classifications, but as a whole blebs in MMC group were much larger, more diffuse and with less vascularity than in OculusGen group. By considering the aforementioned characteristics of bleb, we can expect fewer bleb complications in MMC group and more failure rate in OculusGen group. The complete success rate and the IOP level at all time points of study was better in MMC group. Therefore, MMC can be a better option specially on those who need a lower IOP and also in poor compliant patient for anti-glaucoma medications. The reason for difference in the results of the two groups may not be related only to the type of anti-fibrotic agent. The technique of surgery was somehow different in these two surgeries. In trabeculectomy with MMC we used releasable sutures but in OculusGen we secured the scleral flap by one loose suture at the middle of flap, also we applied MMC not only under the conjunctiva but also under the scleral flap (OculusGen was placed only under the conjunctiva). These factors might also have affected the final results. In this study we tried to use the conventional or recommended method of surgery in each group. One of the main drawbacks of OculusGen needs to be mentioned is the higher cost of this material in comparison to MMC.

Larger number of patients with longer duration of follow-up is required to be certain about the role of this new bioengineered material on the success rate of trabeculectomy.

Conclusion

In conclusion, although trabeculectomy with OculusGen is a safe and effective procedure in patients with glaucoma, but the IOP in MMC group was lower than OculusGen group and significant number of patients in OculusGen group required IOP lowering medications after the surgery.

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