

# Evaluation of Subconjunctival Oculusgen Implantation as an Adjunct to Trabeculectomy

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## Abstract

**Purpose:** To evaluate the efficacy and safety of subconjunctival oculusgen implantation when used during trabeculectomy

**Methods:** In this prospective, nonrandomized, interventional case series, 10 eyes of 10 patients with medically uncontrolled open angle glaucoma were enrolled. Conventional fornix based trabeculectomy with implantation of subconjunctival biodegradable collagen implant (oculusgen) was performed in all patients. The preoperative best corrected visual acuity (BCVA), intraocular pressure (IOP) measurement and numbers of antiglaucoma medication were recorded. There were 7 postoperative follow-up visits within 6 months after surgery. After 6 months, follow-up visits were continued every 2-3 months. At each visit, the examination included measurements of BCVA and IOP, slit-lamp biomicroscopy, assessment of cell and flare, bleb evaluation and funduscopy. Any complications were recorded at the end of each examination. Data analysis was performed using SPSS software version 15.

**Results:** Mean duration of follow-up was 11.9 months (range 6-26 months). Mean preoperative IOP was 19.3 mmHg (range 12-25 mmHg) with 2.9 number of IOP lowering medications (range 2-4) and mean postoperative IOP was 15.3 mmHg (range 10-24) at month 6 (P=0.028) and 14.7 (range 10-20) at last visit (P=0.016). Mean IOP lowering medications and IOP reduction after 180 days were 0.4 (range 0-3) (P=0.000) and 4.2 mmHg respectively. Mean IOP lowering medications and IOP reduction at last visit were 0.7 (range 0-3) (P=0.000) and 4.8 mmHg. Overall success at last follow-up was 80%. None of the patients experienced systemic or ocular complication related to oculusgen.

**Conclusion:** Trabeculectomy with implantation of oculusgen is a safe and effective surgical method in patients with open angle glaucoma, but longer duration of follow-up in larger number of patients is needed.

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

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## Introduction

The main cause of failure of trabeculectomy which is the most common glaucoma surgery is postoperative subconjunctival scarring in the filtering bleb, 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.<sup>1,2</sup>

Most of the currently used adjuncts that modulate wound healing are 5 fluorouracil (5-FU) and mitomycin C (MMC) which are effective in limiting the scarring process, however, these agents can cause adverse effects such as hypotony with maculopathy, cystic thin avascular bleb, bleb leakage, bleb infection and endophthalmitis.<sup>3,4</sup>

The biodegradable collagen matrix implant, marketed initially as OculusGen™ (oculusgen biomedical Inc, 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. This theoretically results in decreased scar formation and improved surgical success over trabeculectomy performed without the adjunctive use of antifibrotic agents. Preliminary studies have 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.<sup>5</sup> Since published data regarding this implant and its role in trabeculectomy is limited, this study was conducted to find more information about this new material and its effect on trabeculectomy surgery.

## Methods

In this prospective, nonrandomized, interventional case series, 10 eyes of 10 patients with the diagnosis of primary open angle or pseudoexfoliation glaucoma that was not controlled and/or tolerated the medication and required trabeculectomy were enrolled.

Exclusion criteria were history of prior ocular surgery or uveitis, pregnancy or breast feeding, patients younger than 18 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 Iran University of Medical Sciences approved the study.

Conventional trabeculectomy with fornix based conjunctival flap and trapezoid scleral flap at supranasal quadrant was performed under general anesthesia.

After sclerostomy and peripheral iridectomy, scleral flap was closed by one 10-0 nylon suture at the center of the flap and then oculusgen (Figure 1) was implanted over the flap.



**Figure 1.** Collagen-glycosaminoglycan matrix which used in our study  
4 mm±0.3 mm (Height)  
7.0±0.5 mm (Diameter)

At the end of surgery drainage of fluid was checked by injecting BSS from stab incision and 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 which tapered off slowly in 6-8 weeks. No antifibrotic agents like MMC or 5-FU were administered during the follow-up.

The preoperative best corrected visual acuity (BCVA), intraocular pressure (IOP), and numbers of antiglaucoma medications were recorded. At each postoperative visit, the examination included measurement of BCVA, IOP measurement by a calibrated applanation tonometer, slit-lamp biomicroscopy, assessment of cell and flare, bleb evaluation and funduscopy. Table 1 shows patient characteristics.

**Table 1.** Patients characteristics (n =10)

Characteristics	No. (%) of patients
<b>Age</b>	
Mean	57.4 years
Range	43-76 years
<b>Gender</b>	
Male	6 (60)
Female	4 (40)
<b>Laterality</b>	
Right eye	5 (50)
Left eye	5 (50)
<b>Preoperative best corrected visual acuity</b>	
Mean	0.82 logMAR
Range	0-3 logMAR
<b>Preoperative intraocular pressure</b>	
Mean	19.3 mmHg
Range	12-25 mmHg
<b>Number of preoperative IOP lowering medications</b>	
Mean	2.9
Range	2-4
<b>Glaucoma type</b>	
Primary open angle	9 (90)
Pseudoexfoliative	1 (10)

Any complications were recorded at the end of each examination.

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  $\pm 10$  days was allowed for the 30, 60, 90 day visits and one of  $\pm 14$  days was allowed for the 180 day visit. After 6 months, follow-up visits were continued every 2-3 months. Mean duration of follow-up was 11.9 months (range 6-26 months). At the end of the study data analysis was performed using SPSS software version 15.

Complete success was defined as an IOP lower than 21 mmHg without antiglaucoma medication and at least 20% reduction of preoperative IOP at the last visit.

Qualified success was defined as:

1. Postoperative IOP lower than 21 mmHg with antiglaucoma medication in patients with preoperative IOP > 21 mmHg
2. Postoperative IOP equal or above 21 mmHg but reduction of IOP at least 30% from baseline with or without antiglaucoma medication in patients with preoperative IOP > 21 mmHg (maximum

number of IOP lowering medication should not be more than preoperative.)

3. Postoperative IOP lower than or equal to preoperative IOP and at least reduction of 2 IOP lowering drugs in patients with preoperative IOP  $\leq 21$  mmHg

Cumulative success was the sum of Qualified and Complete success.

Failure of treatment was defined as IOP less than 5 mmHg or higher than 21 mmHg but with IOP reduction of less than 30% from baseline with antiglaucoma medication at last visit or requirement for reoperation according to defined target pressure or cases which did not meet our success definition.

## Results

In this prospective study 10 patients (6 males and 4 female) with mean age of 57.4 years (range 43-76 years) were enrolled. Mean duration of follow-up was 11.9 months (range 6-26 months).

Mean preoperative BCVA was 0.82 (range 0-3) logMAR and mean postoperative BCVA at month 6 was 1.07 (P=0.061) and at last visit was 1.01 (P=0.141) (range 0-4). Mean preoperative IOP was 19.3 mmHg (range 12-25 mmHg) with 2.9 number of IOP lowering medications (range 2-4) and mean postoperative IOP was 9.14 mmHg (range 8-10) on day 1, 10.3 mmHg (range 4-22) on day 7, 15.33 mmHg (range 10-22) at month 1, 14.9 mmHg (range 10-28) at month 3; 15.3 mmHg (range 10-24) at month 6 and 14.7 (range 10-20) at the last visit.

Table 2 shows IOP of each patient and figure 2 represents range and mean of IOP during follow-up.

Differences of preoperative and postoperative IOP at month 6 and at the last visit were statistically significant (P=0.028 and P=0.016).

Mean IOP reduction at the end of month 6 and at the last visit were 4.2 mmHg and 4.8 mmHg respectively.

Mean IOP lowering medications at the end of month 6 and at the last visit were 0.4 (range 0-3) (P=0.000) and 0.7 (range 0-3) (P=0.000).

Table 3, shows the differences between preoperative and postoperative characteristics.

Based on our definitions for success, at month 6 complete success was 40%, qualified

success was 40% and cumulative success was 80%, and at the last visit complete success was 50%, qualified success was 30% and cumulative success was 80%.

None of the patients experienced systemic or ocular complication (such as intraoperative complications, significant intraocular

inflammation, postoperative hyphema, endophthalmitis, flat AC, choroidal hemorrhage, persistent corneal edema and bleb complications) which needed any specific surgical or medical interventions.

Figure 3 shows the bleb morphology at the end of month 8 after surgery.

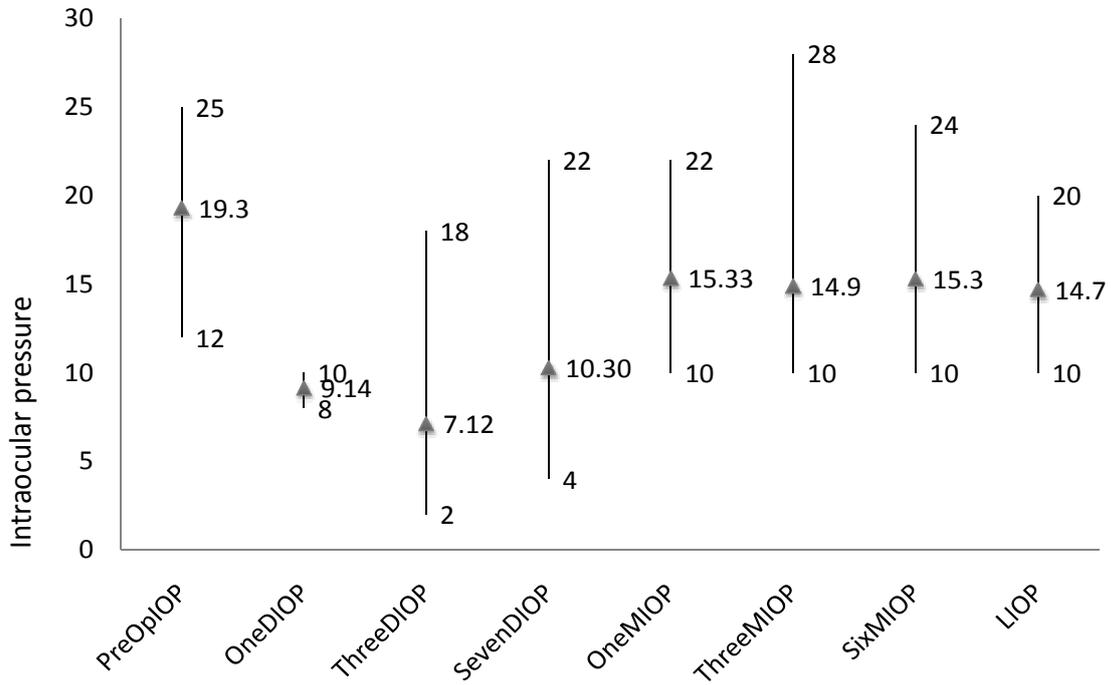
**Table 2.** Shows IOP of each patient during follow-up

Patient	Pre Op IOP	7 DIOP	1 MIOP	3 MIOP	6 MIOP	Last IOP
Case 1	22	12	12	13	12	11
Case 2	18	11	10	14	12	12
Case 3	22	22	20	18	24	16
Case 4	17	10	15	15	14	14
Case 5	12	4	10	15	12	12
Case 6	23	9	11	10	10	10
Case 7	18	4	18	12	18	20
Case 8	16	10	20	12	15	14
Case 9	25	11	22	12	18	18
Case 10	20	10	11	28	18	20

IOP: Intraocular pressure  
 Pre Op IOP: IOP before operation  
 7 DIOP: IOP 7 days after operation  
 1 MIOP: IOP 1 month after operation  
 3 MIOP: IOP 3 months after operation  
 6 MIOP: IOP 6 months after operation

**Table 3.** Comparison of preoperative and postoperative characteristics

Characteristics	Preoperative	Postoperative (at the end of month 6)	Last follow-up
<b>Best corrected visual acuity</b>			
Mean	0.82 logMAR	1.07 logMAR (P=0.061)	1.01 logMAR (P = 0.141)
Range	0-3 logMAR	0-4 logMAR	0-4 logMAR
<b>IOP</b>			
Mean	19.3 mmHg	15.3 mmHg (P=0.028)	14.7 mmHg (P=0.016)
Range	12-25 mmHg	10-24 mmHg	10-20 mmHg
<b>Number of IOP lowering medications</b>			
Mean	2.9	0.4 (P=0.000)	0.7 (P=0.000)
Range	2-4	0-3	0-3



PreOpIOP: IOP before operation  
 OneDIOP: IOP 1 day after operation  
 ThreeDIOP: IOP 3 days after operation  
 SevenDIOP: IOP 7 days after operation  
 OneMIOP: IOP 1 month after operation  
 ThreeMIOP: IOP 3 months after operation  
 SixMIOP: IOP 6 months after operation  
 LIOP: IOP at last visit

**Figure 2.** Shows mean and range of IOP preoperative and during follow-up.



**Figure 3.** A case of trabeculectomy with ocusgen 8 months after surgery

## Discussion

The conventional surgery for glaucoma is trabeculectomy which involves creating a drainage channel to redirect the flow of aqueous out of the eye.

The wound healing response is the most important determinant of the final IOP after trabeculectomy with excessive postoperative scarring significantly reducing success.<sup>1,2</sup> During the past 20 years based on advances in molecular and cellular biology many new agents as modulators of the scarring has been proposed for use as an adjunct to glaucoma surgery.

Since 1980's antiscarring antimetabolites such as 5-FU and MMC are widely used to augment the success of trabeculectomy.<sup>6</sup>

Both MMC and 5-FU reduce fibroblast proliferation in the subconjunctival space as well as in the tenon capsule.<sup>7,8</sup> They are used in trabeculectomy to prevent episcleral fibrosis of the filter. The pyrimidine base analog 5-FU is incorporated into replicating nucleic acid strands and is active only in the synthesis phase of the cell cycle. When applied via postoperative subconjunctival injections, it has been shown to improve the success rate of trabeculectomy.<sup>9</sup> MMC, an antibiotic secreted by streptomyces caespitosus, acts as an alkylating agent that inhibits the synthesis of protein and DNA. MMC also has potent antiangiogenic properties.<sup>10</sup>

Katz GJ et al confirmed this in study on high-risk filtering procedures, they reported that pressure lowering effect was more persistent with MMC than with 5-FU, with a mean follow-up of 32 months.<sup>11</sup> The success rate of trabeculectomy without antifibrotic with 3 months to 5 years follow-up has been reported from 68% to 95.4%.<sup>12-16</sup>

According to different studies the success rate of trabeculectomy with MMC with 3 months to 3 years follow-up has been reported from 62% to 93%.<sup>17-19</sup>

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 which predisposing the eye to infection. Other complications include over-filtration leading to hypotony and maculopathy and reduction of vision. 5-FU is also associated with corneal epithelial toxicity leading to tearing, discomfort and blurred vision.<sup>11</sup> MMC also has

complications such as ciliary body damage (resulting in hypotony), corneal endothelial cell damage and limbal stem cell deficiency.<sup>20-22</sup>

These complications lead to the continued search for alternative intraoperative antiscarring treatment. One of these modalities which has been introduced during the past few years is oculusgen. This is a biodegradable collagen glycosaminoglycan matrix (biodegradable within 30-90 days) which occupies subconjunctival space by its volume and guide the fibroblast growth randomly inside the matrix.<sup>23</sup>

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; Jul 18-21, 2007; Singapore).

Chen et al in a multi-center, prospective and nonrandomized study, found 58.3% reduction in mean IOP 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 antiglaucoma medications and postoperatively, the mean IOP at last follow-up was 16.1±3.2 mmHg with 0.3±0.2 antiglaucoma medications. There was no intraoperative or postoperative complication. (Chen HSL, Hsu WC. Clinical experience with biodegradable 3D-porous collagen glycosaminoglycan scaffold (OculusGen) for treatment of refractory glaucoma. Poster presented at the: Southeast Asian Glaucoma Interest Group; December 1, 2006; Chennai, India). In our study with nearly the same period of follow-up the mean IOP reduction was 23.8% which was not as good as their reports but the number of postoperative antiglaucoma medication was the same.

Scott et al, account the 1 and 2 years success rate of trabeculectomy with MMC in 68 patients (85.4% and 77.9%, respectively). The mean IOP was reduced from 26.3 to 11.3 mmHg at 1 year and to 11.9 mmHg at 2 years

with 88.2% of patients off medication at 1 year and 83.9% of patients off medication at 2 years. Endophthalmitis occurred in 2 (2.2%) of the patients, and hypotonia requiring revision occurred in 4 (4.5%) of the patients.<sup>24</sup> In our study with shorter duration of follow-up the mean IOP reduction was 4.2 mmHg that is significantly less than their results and only 60% of our patients were off medication, 6 months after surgery.

Sanjay et al in one study reported that in patients that underwent trabeculectomy with MMC mean antiglaucoma medication reduced from 2.86 (preoperative) to 0.77 and mean IOP reduced from 26.12 (preoperative) to 15.51 (at month 6 after operation). This study showed complications such as 1% hypotonus maculopathy, 20% hyphema, 3% late postoperative corneal edema, 1% uveitis, 2% suprachoroidal hemorrhage, 1% vitreous hemorrhage, 1% endophthalmitis and 1% choroidal detachment.<sup>25</sup> The mean preoperative number of antiglaucoma medications in our patients was 2.9 which was reduced to 0.4 that is comparable with their results but in contrary to their findings we did not encounter to any significant complications.

Cheung JC et al evaluated the visual and IOP outcome in 157 eyes after trabeculectomy with adjunctive MMC 1 to 3 years after surgery. The mean preoperative IOP was  $29.4 \pm 10.3$  mmHg. This was reduced to  $13.0 \pm 7.6$  mmHg at 1 year,  $11.5 \pm 6.4$  mmHg at 2 years, and  $13.4 \pm 7.3$  mmHg at 3 years. Cumulative success rate was 94.2% at 1 year, 92.1% at 2 years, and 88.7% at 3 years. Their main complications were cataract formation, hyphema and choroidal detachment, and finally they reported that the IOP reduction after MMC filtering surgery is sustained in the intermediate-term (1 to 3 years) follow-up period.<sup>26</sup> Although the cumulative success rate in our study (80%) is less than their results but rate of complication in trabeculectomy with MMC seems much more than trabeculectomy with ocusgen.

Our study comprised 10 glaucomatous eyes which underwent trabeculectomy with ocusgen. The clinical safety and tolerability was represented by absence of signs of local toxicity or intraocular inflammation. The cumulative success rate was 80% and mean

antiglaucoma medication reduced from 2.9 (preoperative) to 0.4 (at month 6 after operations) and mean IOP reduced from 19.3 preoperatively to 15.3 at month 6 (20.7% reduction in IOP) and to 14.7 at the last visit (23.8% reduction in IOP).

Our average preoperative IOP was less than 21 because 6 out of 10 cases had an IOP less than 21 and surgery was done because of noncompliance and/or some allergic reactions to medications. In comparison to the most of the studies which mentioned before of trabeculectomy with MMC with the same duration of follow-up our cumulative success rate (80%) is close to them. So it seems, at least in short term, that implantation of ocusgen during trabeculectomy has nearly a similar effect on IOP reduction.

The main drawback of ocusgen is its cost, which is more than 100 times of MMC. Regarding the complications, we did not find early postoperative complications like, bleb leak, flat AC or choroidal detachment, and also at the last visit no signs of bleb avascularity, blebitis, endophthalmitis or symptoms of bleb dysesthesia was found.

One of the advantages of this surgery is the shorter duration of it; although we did not compare the duration of this surgery with group of MMC, but the surgeon (N.N) feels it is at least 30% faster than the conventional trabeculectomy with MMC.

Limitations of this series are its very small number of operated eyes, short duration of follow-up, and the lack of control group of trabeculectomy with other widely accepted antifibrotic agents like MMC. So our suggestion is to conduct a randomized clinical trial study with larger number of eyes and longer duration of follow-up, which can reveals more about the safety and the efficacy of ocusgen.

## Conclusion

Trabeculectomy with implantation of ocusgen is a safe and effective surgical method in patients with open angle glaucoma, but longer duration of follow-up in larger number of patients is needed.

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