

A COMPARATIVE STUDY BETWEEN TRABECULECTOMY WITH MITOMYCIN-C VERSUS TRABECULECTOMY WITH OLOGEN FOR PATIENTS WITH PRIMARY ANGLE CLOSURE GLAUCOMA

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ABSTRACT

Introduction: Wound healing and scar formation after trabeculectomy may result in fibrosis of the bleb and obstruction of the drainage fistula, eventually leading to bleb failure. Hence, the inhibition of scar formation during the wound-healing process should promote greater success. Recently, tissue-engineered biodegradable implant (Ologen) has been created as an alternative augmentation in trabeculectomy with much less complications.

Purpose: The aim of this study is to compare the result and safety of trabeculectomy with Ologen vs. with MMC in patients with Primary angle closure glaucoma. **Patients and methods:** 48 eyes of 30 patients were undergone subcleral trabeculectomy; 24 eyes with MMC (control group) and 24 eyes with Ologen (study group) and followed-up for one year. The success is by maintaining IOP equal to or less than 21 mmHg without anti-glaucoma eye drops all over the period of follow-up. **Results:** There were no significant differences between the groups in terms of age, gender, type of glaucoma and preoperative IOP. Mean IOPs for both groups were significantly lower than preoperative levels at all intervals ($P < 0.001$). At last visit, the mean postoperative IOP was 15.87 ± 4.1 mmHg in MMC group and 16.17 ± 4.3 mmHg in Ologen group with P-value ($P = 0.806$). The success rate was 87.5% (21/24) in MMC group and 83.3% (20/24) Ologen group. The incidences of early post-operative complications were similar in the 2 groups. **Conclusion:** the success of trabeculectomy with Ologen is lower than that achieved by trabeculectomy with MMC but with no statistically significant difference. However, this implant could be a safe and effective alternate to MMC with almost similar long-term success rate.

KEYWORDS: trabeculectomy, Ologen,

INTRODUCTION

Angle-closure glaucoma (ACG) is a group of diseases in which there is reversible (appositional) or adhesional (synechial) closure of the anterior-chamber angle. The angle closure may occur in an acute or chronic form. In the acute form, the IOP rises rapidly as a result of relatively sudden blockage of the trabecular meshwork (TM) by the iris via papillary block mechanism. The chronic form may develop after acute angle closure where synechial closure of the angle persists, or it may develop over time as the angle closes from prolonged or repeated contact between the peripheral iris and the TM, which often leads to peripheral anterior synechiae (PAS) and functional damage to the angle.^[1]

Trabeculectomy, introduced by Cairns in 1968, remains the standard surgical procedure for the reduction of intraocular pressure (IOP) in patients with medically uncontrolled glaucoma worldwide.^[2,3] Conjunctival scarring is one of the difficulties long associated with glaucoma surgeries such as trabeculectomy. This part of the healing response can undo the benefits of the

glaucoma surgery by closing down the channels created to allow aqueous to escape and thus reduce intraocular pressure. For that reason, minimizing scarring has become an important part of these surgeries. One of the most effective ways to control scarring has turned out to be through the application of mitomycin-C.^[4]

Mitomycin-C (MMC) is an anti-neoplastic/ antibiotic agent isolated from soil bacterium *Streptomyces caespitosus*. It is an alkylating agent that acts by inhibiting DNA synthesis, and inhibiting fibroblast proliferation. It is used intravenously to treat upper gastro-intestinal tumors, anal cancer, breast cancer and bladder tumors. In eye surgery, it is applied topically to prevent recurrence in pterygium surgery, to prevent scarring during glaucoma filtering surgery and haze after Photorefractive keratectomy (PRK) or Lasik. MMC was first used in ophthalmology in 1969 in Japan, where recurrent pterygia were successfully treated with the drug. Its use and application in ophthalmology has been increasing because of its modulatory effects on wound healing.^[5]

With the introduction of adjunctive anti-metabolites, such as 5-fluorouracil (5-FU) and mitomycin-C (MMC), which significantly decrease the post-operative sub-conjunctival scarring, have improved the long term success of trabeculectomy.^[6,7,8,9] However, the use of adjunctive anti-metabolites during surgery have increased the incidence of bleb-related complications like thin avascular blebs, hypotony maculopathy, blebitis, and endophthalmitis.^[10,11,12]

Ologen is an artificial porcine extracellular matrix, which is made of atelocollagen cross-linked with glycosaminoglycan. It is a biodegradable scaffolding matrix that induces a regenerative wound-healing process in the absence of antifibrotic agents. It is designed to prevent episcleral fibrosis and subconjunctival scarring and minimize the random growth of fibroblasts, instead promoting their growth through the pores in the matrix. The implant not only acts as a reservoir but also helps to mechanically separate the conjunctiva and episcleral surface and prevent adhesions between them.^[13] This implant is found to be biodegradable within 90-180 days.^[14] After degradation, the implant leaves behind a loose alignment of collagen fibers inside the bleb, which are remarkably similar to normal tissues.^[15]

In fact, it should induce fibroblasts and myofibroblasts to grow randomly into its porous structure and secrete a loose connective matrix, reducing the scarring degree. The implant inhibits scar formation by acting as a spacer and prevents the fibroblasts from lying down in organized fashion.^[16]

The purpose of this study was to compare the outcomes of trabeculectomy with Ologen implant and trabeculectomy with MMC in patients requiring glaucoma surgery for uncontrolled IOP regarding IOP, bleb function and postoperative complications.

PATIENT AND METHODS

This was a prospective, randomized study conducted at a Public hospital, at Al-Azhar University (Bab-Elsheryia) hospital. Forty eight eyes of 30 patients presented by primary angle closure glaucoma. All the subjects were explained the benefits and risks of the procedure, the composition, and the source of the Ologen implant before obtaining an informed written consent.

Inclusion criteria included individuals' ≥ 18 years of age with medically uncontrolled primary angle closure glaucoma (PACG) with no previous intraocular surgery.

PACG was defined in the presence of an occludable angle on gonioscopy (posterior trabecular meshwork not seen in at least 180° of the total circumference of the angle in primary position).

Exclusion criteria included other types of glaucoma, age < 18 years, previous surgical interventions or laser

procedures and patients unable or unwilling to be followed up for an extended period postoperatively.

After enrollment, patients were randomized into 1 of the 2 groups; Trabeculectomy with Ologen implant was group 1 (study group), and trabeculectomy with MMC was group 2 (control group). All the surgeries were performed by the same surgeon with the same technique.

For each patient the following data were collected preoperatively: age, gender, type of glaucoma and IOP (as measured the day before surgery). The IOP was measured using Goldmann Applanation Tonometer and air puff. Gonioscopy was performed under appropriate testing conditions (e.g. clear cornea). The operative data included surgical technique and presence of any intraoperative complications, also recorded.

Surgical Technique

All surgeries were done by the same technique. Under peribulbar anesthesia, a superior rectus bridle suture was applied with 4-0 silk and fornix-based conjunctival flap at the superior limbus was dissected. A 4×4 mm triangular, partial thickness scleral flap was reflected, a trabeculectomy of 2×2 mm was performed, and a peripheral iridectomy was completed. The scleral flap was closed with single 10-0 Nylon suture at the apex, and conjunctiva was secured with two 8-0 Vicryl wing sutures. The eyes divided into two groups; Ologen group a $6 \text{ mm} \times 2 \text{ mm}$ Ologen implant was placed on top of the sclera and the conjunctiva was then closed. The MMC Group had soaked sponges in MMC (0.2 mg/ml) placed sub-conjunctivally over a wide area for 2 minutes (before creation of the superficial scleral flap). The sponges were removed, and the area was copiously irrigated with ringer lactate.

Postoperative medications and follow up

Postoperatively, all patients were treated with prednisolone acetate 1% eye drops in tapering doses over 4 weeks, antibiotic eye drops 4 times/day for a 2 weeks and cyclopentolate 1% eye drops 3 times/day for 2 to 3 weeks.

Post-operative visits were scheduled at day 1, day 7, 1 month, 3 months, 6 months, and 1 year. At each visit, BCVA, IOP, gonioscopy and complications were recorded.

The definition of success was as follows

1. Full success: IOP less than 18 mmHg without medications.
2. Satisfactory success: IOP less than 18 mmHg with medications.
3. Failure: IOP more than 18 mmHg with medications.

Hypotony was defined as IOP equal or less than 6 mmHg.

Statistical analyses

Statistical analysis was performed using SPSS for Windows (SPSS Inc., Chicago, Illinois, USA). P-values of < 0.05 were considered statistically significant.

RESULTS

48 eyes of 30 patients were included in this study and divided randomly into two groups using the random number table; 24 were assigned to receive Ologen implant on top of the scleral flap subconjunctivally

(study group) and 24 were assigned to undergo trabeculectomy with addition of mitomycin (control group). All patients completed the study at one year visit. Demographic characteristics and preoperative data are presented for both groups in (Table 1).

There were no significant differences between the groups in terms of age, gender, eye laterality and preoperative IOP.

Table 1: Demographic characteristics of the study.

		Study group	Control group	P- value
No. of eyes		24	24	
Age (years)		61.3±9.74	63.7±11.26	0.434
Gender	Male	14 (58.3%)	13 (54.17%)	0.998
	Female	10 (41.7%)	11 (45.83%)	
Eye laterality	Rt.	13 (54.17%)	12 (50%)	0.999
	Lt.	11 (45.83%)	12 (50%)	
Preoperative IOP		34.47±6.83 mmHg	36.18±9.37 mmHg	0.474

Among operative procedure “subscleral trabeculectomy” there is no recorded intra-operative complications in both groups.

Postoperative IOP levels were significantly lower than preoperative levels for both groups at all intervals (P< 0.001).

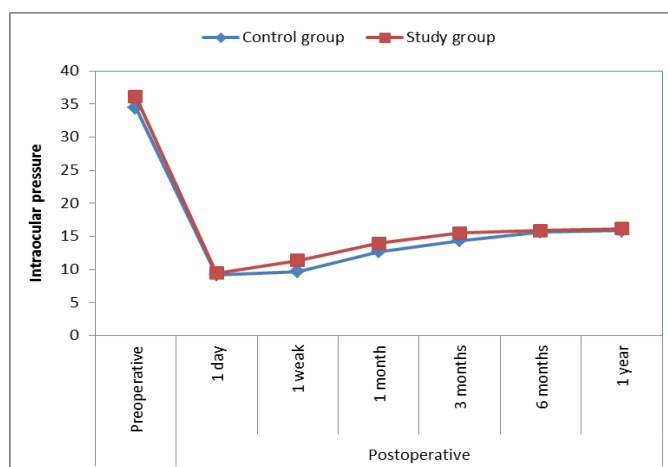
Mean IOPs for both groups at all visits are listed in (Table 2) (Fig. 1). No statistically significant difference in IOP was observed between the two groups at all visits.

Success rate was 87.5% (21/24) in MMC group (Fig. 2) and 83.3% (20/24) Ologen group (Fig. 3), which had no statistically significance difference (P= 0.997).

Table 2: Mean intraocular pressure preoperatively and at follow-up visits for study.

		Control group	Study group	P- value
Preoperative		34.47±6.83 mmHg	36.18±9.37 mmHg	0.474
Postoperative	1 day	9.21±2.8** mmHg	9.47±3.1** mmHg	0.762
	1 week	9.67±3.5** mmHg	11.34±3.9** mmHg	0.125
	1 month	12.66±2.4** mmHg	13.93±5.7** mmHg	0.321
	3 months	14.37±4.3** mmHg	15.52±6.2** mmHg	0.459
	6 months	15.69±4.6** mmHg	15.88±4.8** mmHg	0.889
	1 year	15.87±4.1** mmHg	16.17±4.3** mmHg	0.806
Success rate		21/24 (87.5%)	20/24 (83.3%)	0.997

**P-value < 0.001 highly significant.

**Fig. 1: Intraocular pressure difference over the periods in both groups.**

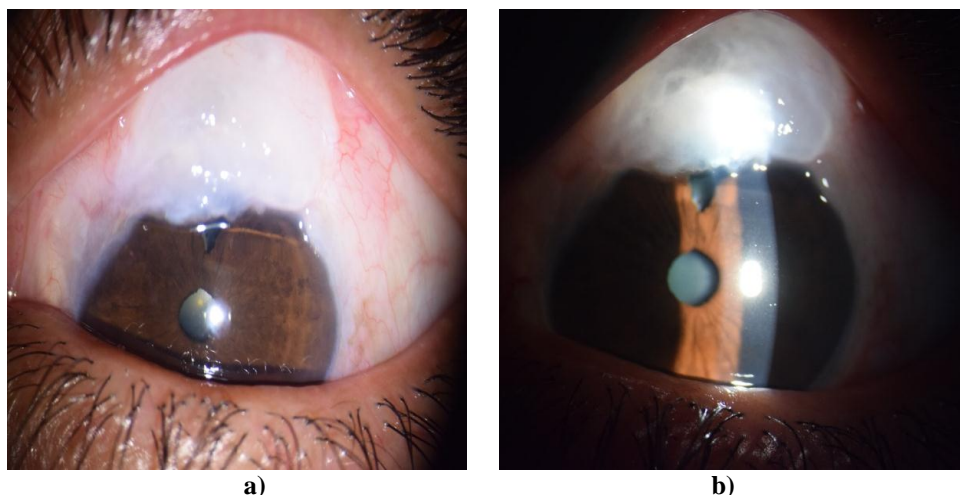


Fig. 2: (a, b) Bleb in a case of control group, (large avascular polycystic bleb).

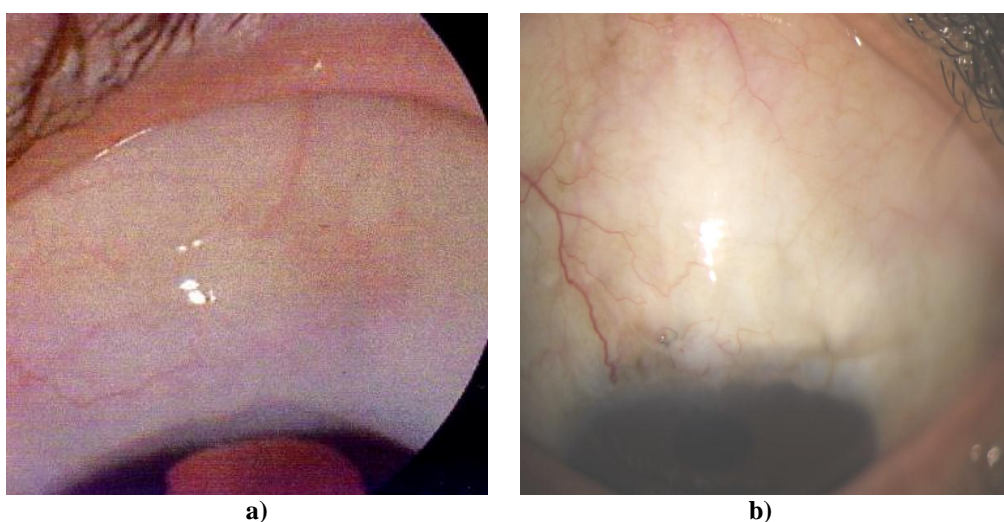


Fig. 3:(a,b) Bleb in a case of study group.

Postoperative complications were reported in both group as in (table 3), an avascular thin bleb was recorded in two eyes in control group 2/24 (8.3%). Hypotony with flat anterior chamber (AC) was reported in three eyes in control group 3/24 (12.5%), while in study group, shallow AC was recorded in one eye 1/24 (4.2%) but without hypotony. In the study group, four eyes had a mild hyphema 5/24 (20.8%). Flat fibrosed bleb was recorded in four eyes in study group 4/24 (16.7%), while in control group, it was recorded only in three eyes 3/24

(12.5%) (Failure rate). Bleb leak (positive seidel test) was reported in two eyes 2/24 (8.3%) in control group. AC reaction was reported in seven eyes 7/24 (29.17%) in control group, and nine eyes 9/24 (37.5%) in study group. As regard reported complications, there were no statistically significance differences between both groups except hyphema which had a significant difference in study group ($P= 0.048$). No other major complication was seen as endophthalmitis.

Table 3: Postoperative complications for the study.

Complications	Control group	Study group	P- value
Avascular thin polycystic bleb	2/24 (8.3%)	0/24 (0%)	0.473
Shallow AC	3/24 (12.5%)	1/24 (4.2%)	0.605
Hypotony	3/24 (12.5%)	0/24 (0%)	0.233
Hyphema	0/24 (0%)	5/24 (16.7%)	0.048*
Flat fibrosed bleb	3/24 (12.5%)	4/24 (16.7%)	0.997
Bleb leak	2/24 (8.3%)	0/24 (0%)	0.473
AC reaction	7/24 (29.17%)	9/24 (37.5%)	0.759
Failure rate	3/24 (12.5%)	4/24 (16.7%)	0.997

AC: anterior chamber.

* P-value < 0.05 significant.

DISCUSSION

Trabeculectomy is the most common surgical procedure for the treatment of glaucoma. These procedure is supposed to remove a portion of the trabecular meshwork, and using a partial-thickness scleral flap to cover the sclerostomy, a fistula is created between the anterior chamber and the subconjunctival space. In the early postoperative period, excessive aqueous filtration could cause low IOP. Severe hypotony could result in several complications such as choroidal detachment, gradual bleb failure, cataract and corneal edema, and can be associated with maculopathy and loss of visual acuity.^[17]

On the other hand, wound healing and scar formation could cause fibrosis and obstruction of aqueous outflow, which is one of the most common reasons for the failure of glaucoma surgery.^[18]

The survival of trabeculectomy improved with the use of intraoperative antimetabolites as an adjuvant. However, the use of mitomycin and 5-FU have been associated with loss of integrity of the conjunctival barrier, resulting in a thin walled avascular drainage bleb, which may lead to hypotony and infection occurring years after trabeculectomy.^[6] Other agents such as corticosteroids, growth-factor inhibition and amniotic membrane have been applied to enhance the results of antiglaucoma surgery.^[20]

Ologen is a biodegradable, porous, porcine, collagen implant. It influences the fibrosis process by guiding the patterns of fibroblast migration and normalizing secreted extracellular matrix deposition. It also helps to separate the conjunctiva and episcleral surface preventing adhesions between them.^[21]

Collagen implants have been used as an adjunct during trabeculectomy to modulate post-operative wound healing in various animal studies with an improved success. They offer the potential for a new means of providing controlled resistance between the anterior chamber and the subconjunctival space in the early postoperative period, as well as maintaining long-term IOP control by avoiding early scar formation and creating a loosely structured filtering bleb.^[21]

In this study, I compared the efficacy and safety of trabeculectomy with Ologen vs. with MMC in patients with Primary angle closure glaucoma. No statistically significance difference in IOP was observed between the two groups at all visits. Postoperative IOP levels were significantly lower than preoperative levels for both groups at all intervals ($P < 0.001$). Success rate was 87.5% (21/24) in MMC group and 83.3% (20/24) Ologen group, which had no statistically significance difference (P). As regard postoperative complications, there were no statistically significance differences between both groups except hyphema which had a significant difference in study group.

Papaconstantinou^[16] et al., reported that; postoperative IOPs for both groups were significantly lower than preoperative levels at all intervals ($P < 0.05$). No statistically significant differences between the two groups were observed in terms of success rate and postoperative complications.

Also, *Senthil^[23] et al.*, found the success rate of trabeculectomy at 6 months was similar in eyes with adjunctive MMC use compared to Ologen. The complete and qualified success probabilities were similar between the 2 groups over all these time points. Also, He found the post-operative complications to be similar in the 2 groups, except for transient hyphema, which was more in Ologen group, which were similar to this study.

Cillino^[24] et al., There was no significant difference in the postoperative behavior between the two groups, with a highly significant and stable IOP reduction and very few antiglaucoma medications throughout the 24-month follow-up, indicating that the efficacy of the Ologen implant is analogous to MMC.

CONCLUSION

The results of this study suggested that the Ologen implant could be a new, safe, and effective alternative to MMC, with similar long-term success rate.

RECOMMENDATION

Due to the relatively small sample size, which limits the statistical comparison between the groups, further larger randomized trials are required to investigate the long-term efficacy and safety of this new device.

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