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Research Article

Comparative Study of Filtering Surgeries with Ologen and Mitomycin- C versus Mitomycin-C Alone

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Abstract

Purpose: To compare the efficacy and safety of filtering surgeries using an Ologen implant combined with mitomycin C versus filtering surgeries with mitomycin C alone.

Methods: Retrospective comparative study of 38 filtering surgeries with Ologen and mitomycin C against 40 filtering surgeries with mitomycin C. Trabeculectomies and deep sclerectomies, combined or not with phacoemulsification, were both accepted. Intraocular pressure values, the number of antiglaucoma medications used and complications were analysed for a 12-month follow-up period. Complete success (intraocular pressure less than 21 mmHg without medications) and qualified success (intraocular pressure less than 21 mmHg with or without medications) were also evaluated. A subgroup analysis regarding the type of surgery was also performed.

Results: During the first year of postoperative follow-up, intraocular pressure was 18% lower in the Ologen group ($p < 0.015$). Regarding the number of antiglaucoma medications needed, there was a major decrease in the Ologen group, with a reduction of 2,89 medications versus 1,95 in the mitomycin C group ($P < 0.001$). Complications were higher in the mitomycin C group, but without reaching levels of significance. In the subgroup analysis, IOP was significantly better in the Ologen group only for deep sclerectomy with phacoemulsification.

Conclusions: The association of Ologen and mitomycin C in filtering surgeries offers good intraocular pressure results, better than mitomycin C alone at least in phaco-deep sclerectomies. Furthermore, this combination allows less need of antiglaucoma medications without increasing the number of complications.

Keywords: *Ologen; Collagen Implant; Mitomycin C; Filtering Surgery; Glaucoma Surgery*

Abbreviations

MMC: Mitomycin- C 5FU 5-Fluorouracil; IOP: Intraocular Pressure ln(IOP) Logarithm of IOP

Introduction

The major challenge for filtering surgery is to overcome subconjunctival and episcleral scarring [1,2]. Therefore, adjunctive antimetabolites, such as mitomycin- C (MMC) and 5- fluorouracil (5FU), are broadly used. These agents prevent scar formation inhibiting fibroblast proliferation, to enhance success rates [3-5].

Ologen (Aeon Astron Europe B.V, The Netherlands) is a biodegradable porcine-derived collagen and glycosaminoglycan matrix, which modifies the wound healing response. This implant provides a scaffold for fibroblasts, which grow through the pores in a random fashion, in order to diminish tissue cicatrisation [6,7]. It was designed with the aim to represent an alternative to antimetabolites. However, two recent meta-analysis have concluded that trabeculectomy with Ologen does not seem to offer any significant advantage compared with trabeculectomy plus MMC [8,9].

Our study was designed to compare the outcomes of filtering surgery using an Ologen implant combined with MMC versus MMC alone. There are many publications comparing these two adjuvants, but just a few comparing filtering surgeries with both adjuvants together against the classical one, just with MMC.

Materials and Methods

This was a retrospective comparative study undertaken in three different centres: Hospital General de Granollers, Hospital Sagrat Cor and Hospital General de Catalunya (Barcelona, Spain) including uncontrolled glaucoma patients who underwent filtering surgery with Ologen implant and MMC or with adjuvant MMC alone. Earlier surgeries were performed just with MMC. From the moment that Ologen was available in our institutions, all surgeries were performed using both adjuvants. Patients with primary open angle glaucoma or primary angle closure glaucoma, pigmentary glaucoma and pseudoexfoliative glaucoma were accepted. Patients with other forms of glaucoma or previous vitreo-retinal surgery were excluded. Trabeculectomies and deep sclerectomies were both included, even the ones with combined phacoemulsification. The surgeries were performed from October 2014 to June 2016 by the same surgeon, J. Suárez, MD. MMC dosage was 0.2 mg/ml in a two minutes application. The Ologen model used was the squared one, of 10 x 10, and 2 mm high (model number 870051), divided into 3 rectangular pieces, placed under the conjunctiva, posterior to the scleral flap. For deep sclerectomy a forth piece of Ologen was placed under the scleral flap, as a space maintainer (Figure 1).

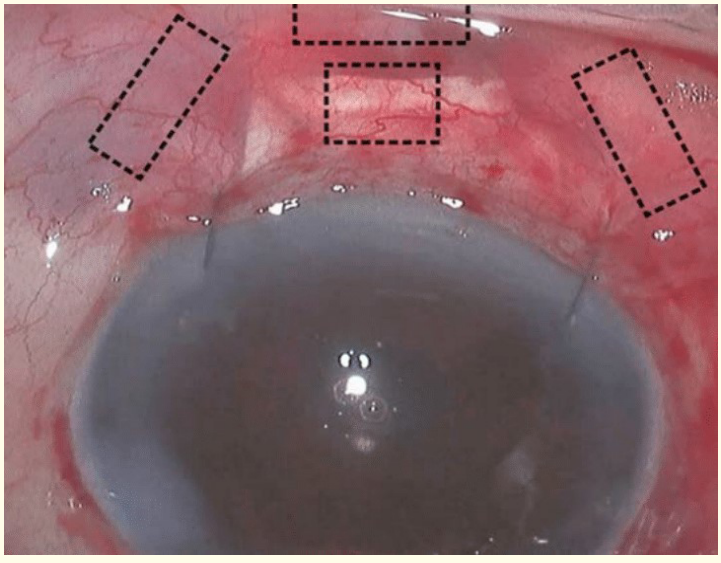

Figure 1: *Intraoperative photograph of a deep slerectomy showing how Ologen is placed (discontinuous rectangles). The implant is cut into several pieces. One piece is placed under the scleral flap, as a space maintainer. Three more pieces are placed separately under the conjunctiva, in order to increase its area of action.*

The preoperative data included: age, gender, type of glaucoma, intraocular pressure (IOP), number of antiglaucoma medications and if they had any previous filtering surgery. The operative data recorded were laterality and type of surgery: trabeculectomy or deep sclerectomy, combined or not with phacoemulsification. Postoperative IOP was registered at 6 points of the follow-up: 1 week, 1 month, 3 months, 6 months, 9 months and 1 year. Complications and the number of postoperative antiglaucoma medications were also noted.

Complete success, defined as IOP less than 21 mmHg without medications, and qualified success, defined as IOP less than 21 mmHg with or without medications, were evaluated at 3 months, 6 months and 1 year after the surgery.

This study complied with the tenets of the Declaration of Helsinki and was approved by the Ethical Committee of Hospital General de Granollers.

Statistical analysis

To check the normal distribution for IOP, histograms and normal probability plots were made for IOP and the natural logarithm of IOP [ln(IOP)] on all measurement times. It turned out that a logarithmically transformed IOP had a good approximate normal distribution, in contrast to IOP itself.

The data were analyzed using a Linear Mixed Model with ln(IOP) as outcome variable. The 6 postoperative ln(IOP) measurements were taken as dependent variables in the model. To adjust for the baseline IOP, the logarithmically transformed baseline IOP measurement was taken as covariate, which means that the model estimates the Ologen effect given the same baseline IOP. Other covariates were treatment group and time of follow-up as categorical, and the interaction between these two. The model estimates the effect of Ologen on the logarithmic scale on every time of follow-up. We also calculated and tested the Ologen effect averaged over the follow-up times. After exponentiation the regression coefficients can be interpreted as the factor by which IOP is higher or lower in the Ologen group compared to the MMC group. In order to adjust for the surgery type, it was added as a factor to the statistical model in a further subanalysis.

To compare the reduction in medications used between groups, we calculated the difference per eye between the number of medications pre and post intervention. To adjust for the correlation between eyes, we compared the average reduction in medication used between the two groups using a generalized estimating equation analysis. To compare complications between the two groups the Fisher's exact test was used. A Kaplan-Meier survival analysis was made for complete and qualified success evaluation. P values under 0.05 were considered statistically significant. All analysis were performed using the SPSS software (SPSS, Inc., Chicago, IL).

Results

78 eyes of 71 patients were enrolled in the study, 38 eyes belonged to the Ologen group and 40 eyes to the MMC group. There were 7 patients who had bilateral surgery, five of them with both eyes contributing in the Ologen group, one patient with both eyes in the MMC group and a patient with one eye in each group. Baseline characteristics of the patients are shown in table 1.

	Ologen group: 38 eyes	MMC group: 40 eyes
Gender	15 females (45,5%) 18 males (54,5%)	14 females (35,9%) 25 males (64,1%)
Mean age	73,03	71,38
Laterality	17 RE (44,7%) 21 LE (55,5%)	19 RE (47,5%) 21 LE (52,5%)
Type of glaucoma	29/38 POAG (76,3%) 4/38 PACG (10,5%) 4/38 PEXG (10,5%) 1/38 PG (2,7%)	31/40 POAG (77,5%) 2/40 PACG (5%) 7/40 PEXG (17,5%) 0/40 PG (0%)
Mean preoperative IOP	19,11 mmHg	20,93 mmHg
Mean number of medications	3,24	2,6
Previous filtering surgery	6/38 (15,8%)	2/40 (5%)

Table 1: *Baseline characteristics of patients.*

RE: Right Eye; LE: Left Eye; POAG: Primary Open Angle Glaucoma; PACG: Primary Angle Closure Glaucoma; PEXG: Pseudoexfoliation Glaucoma; PG: Pigmentary Glaucoma

In the Ologen group 32 eyes underwent trabeculectomy, 11 of them with phacoemulsification and 6 eyes underwent deep sclerectomy, 2 of them with phacoemulsification. In the MMC group there were 31 trabeculectomies, 8 of them with phacoemulsification and 9 deep sclerectomies, 4 of them with phacoemulsification. Chi-square test showed no differences in the distribution of surgery types between the two groups ($p = 0.73$).

All surgeries were performed retrospectively, but part of the follow-up was prospective. In the Ologen group, the last 7 months of follow-up on average, were prospective. On the other hand, in the MMC group, as surgeries were performed earlier, just the last 3 months on average, were prospective. Eight participants did not complete the follow-up period. Four of them belonged to the Ologen group: one suffered a retinal detachment, another one deceased, the third patient, who was participating for both eyes in this group, and the forth one, moved to another city. From the other four patients, who belonged to the MMC group, three had a surgery failure and had to be re-operated and the other one moved to another city.

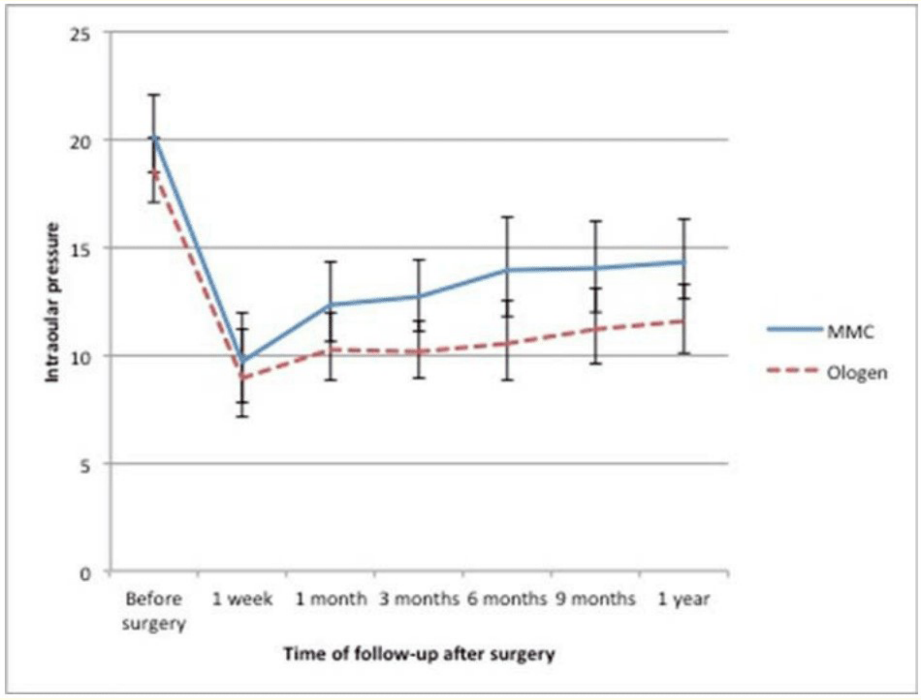

Figure 2: *This graphic shows the median intraocular pressure, preoperative and in different times of the follow-up, for the two groups.*

	Median IOP Ologen group	Median IOP MMC group	Mean percentage of IOP reduction by Ologen effect (95% interval confidence)	P- value	Mean IOP reduction adjusted by surgery type	P-value
Preoperative	18.55	20.18	-	-	-	-
1 week	8.9	9.7	7.7 (-25, 31.8)	0.602	6.9	0.634
1 month	10.3	12.3	16.4 (-2,2, 31.6)	0.079	15.7	0.097
3 months	10.2	12.7	19.6 (4,7, 32.2)	0.013*	18.9	0.018*
6 months	10.5	13.9	24.4 (5.0, 39.9)	0.017*	23.9	0.016*
9 months	11.2	14.0	19.7 (1.8, 34.4)	0.033*	19.2	0.036*
1 year	11.6	14.3	19.0 (3.6, 31.9)	0.020*	18.5	0.023*

Table 2: *Intraocular pressure (IOP) median values and Ologen effect on IOP in different follow-up times.*

** Indicates significant IOP difference between the two groups. P value < 0.05 was considered statistically significant.*

Figure 2 shows IOP results in the two groups. In order to compare them, what was measured was the estimate percentage by which IOP was lower in the Ologen group. As shown in table 2 there is a statistical difference favouring the Ologen group at all points of follow-up beyond the first month. The average IOP during the 12 months was also significantly lower in the Ologen group by an 18.0%. The last two columns of the table correspond to the IOP results adjusted by the surgery type, which were also significantly better for the Ologen group from the third month to the end of the follow-up. In order to analyse the Ologen effect per each surgery type, four subgroup analysis were performed comparing IOP results for Ologen versus MMC for the four different kinds of surgeries included in the study separately. Differences favouring Ologen were only significant for phaco-deep sclerectomy in all measurement times except from 1 week and 9 months and for phaco-trabeculectomy just in the 6-month measurement (Table 3).

	Surgery type	Mean percentage of IOP reduction by Ologen effect (95% interval confidence)	P-value
1 week	Trab	1 (-44, 32)	0.960
	DS	-90 (-315, 13)	0.105
	Phacotrab	30 (-25, 61)	0.221
	PhacoDS	64 (-10, 88)	0.073
1 month	Trab	15 (-12, 36)	0.242
	DS	3 (-66, 44)	0.905
	Phacotrab	14 (-33, 45)	0.487
	PhacoDS	59 (5, 82)	0.037*
3 months	Trab	10 (-14, 29)	0.368
	DS	24 (-19, 51)	0.216
	Phacotrab	30 (-2, 52)	0.065
	PhacoDS	52 (2, 77)	0.045*
6 months	Trab	9 (-20, 32)	0.492
	DS	21 (-43, 56)	0.426
	Phacotrab	37 (2, 60)	0.043*
	PhacoDS	64 (17, 84)	0.018*
9 months	Trab	14 (-13, 34)	0.282
	DS	20 (-39, 54)	0.404
	Phacotrab	19 (-24, 47)	0.332
	PhacoDS	53 (-6, 79)	0.069
1 year	Trab	14 (-9, 32)	0.208
	DS	4 (-53, 40)	0.835
	Phacotrab	24 (-11, 48)	0.147
	PhacoDS	53 (4, 77)	0.039*

Table 3: *Ologen effect on IOP per surgery type in different follow-up times.*

Trab: Trabeculectomy; DS: Deep Sclerectomy; Phacotrab: Trabeculectomy Plus Phacoemulsification; Phaco DS: Deep Sclerectomy Plus Phacoemulsification.

**Indicates significant IOP difference between the two groups. P value < 0.05 was considered statistically significant.*

Regarding the number of antiglaucoma medications needed, there was a major reduction in the Ologen group (P< 0.001). This group started from a mean of 3,24 ± 0.68 medications, which decreased to 0.34 ± 0.75 one year after the surgery. On the other hand, the MMC group needed a mean of 2,6 ± 1.15 medications pre-surgery and ended the year with a mean of 0.65 ± 1.32.

Complications	Ologen group	MMC group	p-value
Hypotony	5/38 (13,2%)	1/40 (2,5%)	0,072
Suturolysis	One suture 4/38 (10,5%) Two sutures 0/38 (0%)	One suture 8/40 (20%) Two sutures 4/40 (10%)	0.089
Needling	Once 3/38 (7,9%) Twice 0/38 (0%) Four times 0/38 (0%)	Once 6/40 (15%) Twice 2/40 (5%) Four times 1/40 (2,5%)	0.092
Goniopuncture	Once 1/38 (2,6%) Twice 0/38 (0%)	Once 4/40 (10%) Twice 2/40 (5%)	0,078
Reinterventions	1/38 (2,6%)	5/38 (13,2%)	0.134
Seidel	0/38 (0%)	2/40 (5%)	0,282
Iris incarceration	0/38 (0%)	3/40 (7,5%)	0.147

Table 4: *Number of complications.*

** P value < 0.05 was considered statistically significant*

The incidence of all kind of complications was lower in the Ologen group, except from hypotony. However, for none of the specific complications the difference between groups was statistically significant (Table 4). We also calculated the number of complications per patient, which was also higher in the MMC group, but without reaching levels of significance. The Ologen group had 0.44 ± 0.61 complications per patient and there were 0.97 ± 1.18 complications per patient in the MMC group (P = 0.063).

The groups were also compared using Kaplan-Meier survival curves (Figure 3 and 4). They show the proportion of patients with uninterrupted success at different time points of the follow-up. The log-rank tests were not statistically significant, P = 0.537 and P= 0.085 for complete and qualified success, respectively.

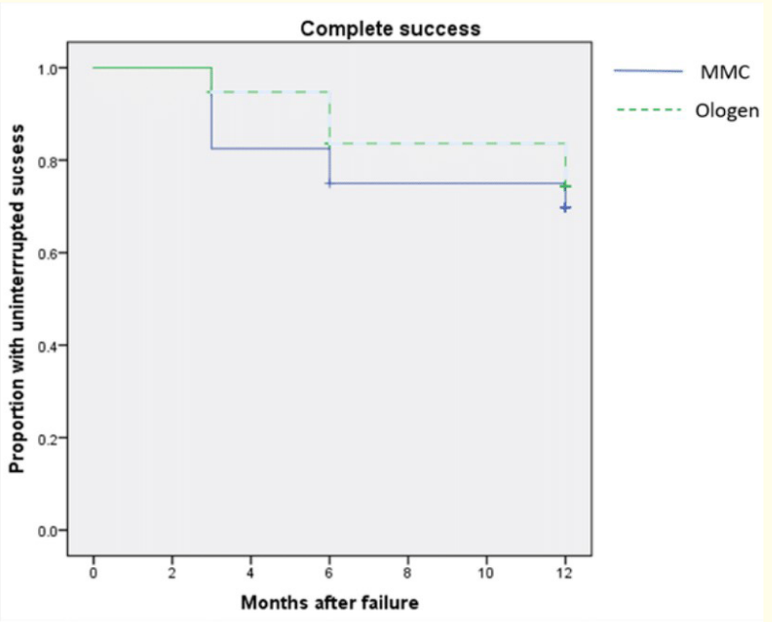

Figure 3: *Kaplan-Meier survival curves for uninterrupted complete success for the two groups.*

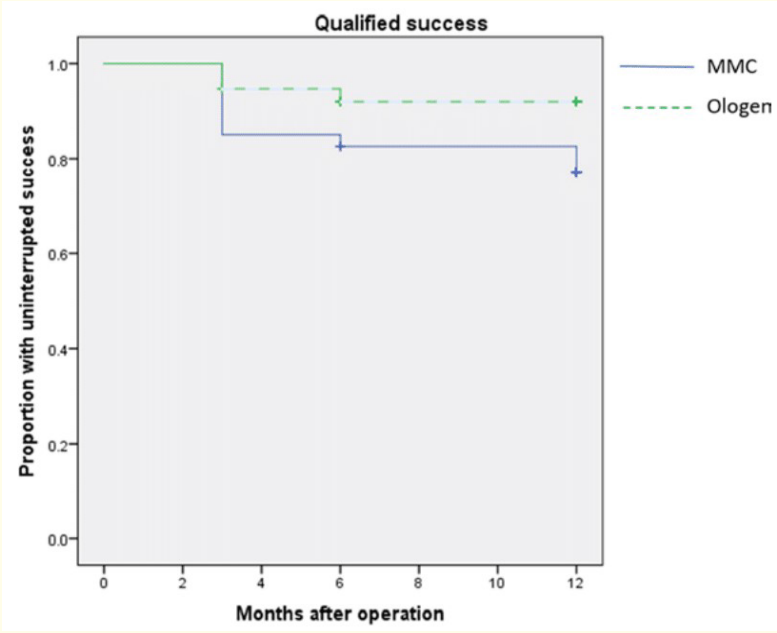

Figure 4: *Kaplan-Meier survival curves for uninterrupted qualified success for the two groups.*

Discussion

The wound healing response is the most important determinant of the final IOP after filtering surgery. Excessive postoperative scarring significantly reduces the success rate [10].

The process of wound healing is composed of two phases: the initial steps in wound healing are inflammation and coagulation, leading to a cascade of biological events including cellular, hormonal and growth factor release. The second phase involves replacement and regeneration by collagen coming from fibroblasts, which is subject to modification with the use of antiproliferative or wound modulatory agents, used either singly or in combination [11,12].

Mitomycin C is a cytostatic antibiotic isolated from Streptomyces caespitosus used originally as a chemotherapeutic agent. It acts independently of the cell cycle to crosslink DNA and inhibit cell synthesis. In glaucoma surgery it is used to inhibit fibroblast proliferation, thus avoiding scar tissue formation [13].

Ologen is a bioengineered collagen matrix obtained from porcine hide. It is made of cross- linked lyophilized type I collagen and glycosaminoglycan with a pore diameter between 10 and 300 microns. This matrix serves as a spacer and a scaffold to modulate the fibrotic response as fibroblasts and myofibroblasts proliferate in response to surgically induced tissue injury. Ologen only functions as a wound modulator and does not have any antiproliferative properties against fibroblasts to counter the scarring response [8].

In summary, MMC and Ologen act on different targets. Therefore, the simultaneous use of both agents could improve surgical results.

There are many publications comparing MMC versus Ologen in trabeculectomy, which are assembled in two meta-analysis, published in 2014 and 2015 by He., *et al.* [8] and Ji., *et al.* [9] respectively. They have both failed to show any differences between these two adjuvants in surgery's outcomes.

There are not many publications with results of filtering surgeries using both adjuvants together. There are three case series, published by Angmo., *et al.* [14], Dada., *et al.* [15] and Kohlhaas [16], joining a sum of 136 trabeculectomies with Ologen and MMC. They describe good IOP results and significant reduction of antiglaucoma medication. Complications were low, with a total of 8 hypotonies, 5 encapsulated blebs, one Seidel and one Ologen extrusion. There are only two comparative studies, published by Menda., *et al.* [17] and Castejón., *et al.* [18], contrasting the use of Ologen plus one antimetabolite versus either Ologen or an antimetabolite alone. Nevertheless, in the former, the antimetabolite used in association with Ologen was 5FU, not MMC, and its application soaking the implant is not the recommended application by the manufacturer. Furthermore, the trabeculectomies were assisted with Ex- press shunts (Alcon, Fort Worth, Texas). Worst results were for surgeries with Ologen alone, although just 8 cases belonged to this group, and no differences were found between surgeries with Ologen plus 5FU versus the ones with MMC. The latter, by Castejón., *et al.* [18], showed better IOP results in phacotrabeculectomies with Ologen plus low dose of MMC (0.1 mg/ml) versus phacotrabeculectomies with low dose of MMC. However, no differences were found between these adjuvants in the trabeculectomy subgroup. There were not significant differences in terms of reduction of antiglaucoma medication in any of the subgroups.

Our study points out that the combination of Ologen and mitomycin C in filtering surgery allows better IOP control, with an average of 18% lower IOP in this group during the first year. Even though no differences were found in the distribution per types of surgery between the two groups, a subgroup analysis comparing IOP results between Ologen and MMC separately, according to the type of surgery performed, was made. Differences were only significant for phaco-deep sclerectomy in almost every measurement time and for phaco- trabeculectomy just for 6-month measurement time. Nevertheless, intervals of confidence were wide, due to the low patient numbers. This results are quite consistent with the ones obtained by Castejón., *et al.* [18], who hypothesize that, as the addition of a phacoemulsification to a filtering surgery leads to a major inflammatory response, the Ologen implant could have helped to diminish the fibrotic response, improving IOP outcomes in this group of patients.

In the overall analysis, Ologen also offered larger reduction of antiglaucoma medications. The major use of hypotensive drops in the MMC group could have also masqueraded stronger differences in IOP outcomes. Complications were low in the two groups. Except from hypotony, all complications were higher in the MMC group, but without statistical significance. Suturolysis may have been lower in the Ologen group because of the difficulty to perform it with the implant covering the suture. Deep sclerectomy was performed more in the MMC group; therefore a higher rate of goniopuncture was expected.

The retrospective nature is the major limitation of our study. However, as Ologen was used in all surgeries beyond the date of its availability, a possible selection bias was avoided. As part of the study follow-up was prospective, there were some patients lost to follow-up. Another limitation is the inclusion of different kinds of surgeries and different types of glaucoma, which has led to a more heterogeneous sample. Furthermore, studies with longer follow-up and major sample should be made in order to confirm these outcomes.

Conclusion

In conclusion, our results suggest that the association of Ologen and MMC in filtering surgery could offer good IOP results, better than MMC alone at least when a phaco-deep sclerectomy is performed. This combination also allows a major reduction of antiglaucoma medications without increasing the number of complications.

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