

Healing: use of collagen matrix

Cicatrização: uso de matriz de colágeno

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ABSTRACT

The Ologen™ collagen matrix is a new antifibrotic agent composed of a porous matrix of type I atelocollagen and cross-linked glycosaminoglycans, which can be used as an alternative for the modulation of healing in surgeries. Because it is highly porous and biodegradable, this implant assists in the physiological repair processes that occur in the connective and epithelial tissue of the lesion without the formation of fibrotic tissue, which leads to surgical failure and IOP elevation. The Trabeculectomy (TREC) is considered the standard surgery for the treatment of glaucoma; however, the surgical success rates in the medium and long term are related to surgical site healing, mainly involving conjunctival and tenonian tissue. The healing process is divided into 4 main phases: coagulative, inflammatory, proliferative and remodeling, with a series of chemical cascades and biochemical factors released in an attempt to restore hemostasis. Since several researches in the literature have already demonstrated the beneficial effects on healing by using the Ologen collagen matrix in ophthalmic surgeries, in addition to possible complications. The results of current Ologen implant studies for the treatment of glaucoma are encouraging and promising. However, future randomized clinical trials with long-term follow-up are necessary to evaluate the safety and efficacy of the new implant in modulating healing, achieving better rates of surgical success.

Keywords: Healing; Glaucoma/surgery; Ologen.

RESUMO

A matriz de colágeno Ologen™ é um novo agente antifibrótico composto por uma matriz porosa de atelocolágeno tipo I e glicosaminoglicanos reticulados, que pode ser utilizado como uma alternativa para a modulação da cicatrização nas cirurgias. Por ser altamente poroso e biodegradável, este implante auxilia nos processos de reparação fisiológicos que ocorrem no tecido conjuntivo e epitelial da lesão, sem a formação de tecido fibrótico, o qual acarreta insucesso cirúrgico e elevação da PIO. A Trabeculectomia (TREC) é considerada a cirurgia padrão para o tratamento do glaucoma, no entanto as taxas de sucesso cirúrgico a médio e longo prazo estão relacionadas a cicatrização do sítio operatório, envolvendo principalmente o tecido conjuntivo e tenoniano. O processo de cicatrização é dividido em 4 fases principais: coagulativa, inflamatória, proliferativa e remodeladora, com uma série de cascatas químicas e fatores bioquímicos liberados na tentativa de restabelecer a hemostasia. Diversas pesquisas na literatura já demonstraram os efeitos benéficos na cicatrização ao utilizar a matriz de colágeno Ologen em cirurgias oftalmológicas, além das possíveis complicações. Os resultados dos atuais estudos com implante de Ologen para o tratamento de glaucoma são encorajadores e promissores. No entanto, ensaios clínicos randomizados futuros com seguimento a longo prazo são necessários para avaliarmos a segurança e a eficácia do novo implante na modulação da cicatrização, alcançando melhores taxas de sucesso cirúrgico.

Descritores: Cicatrização; Glaucoma/cirurgia; Ologen.

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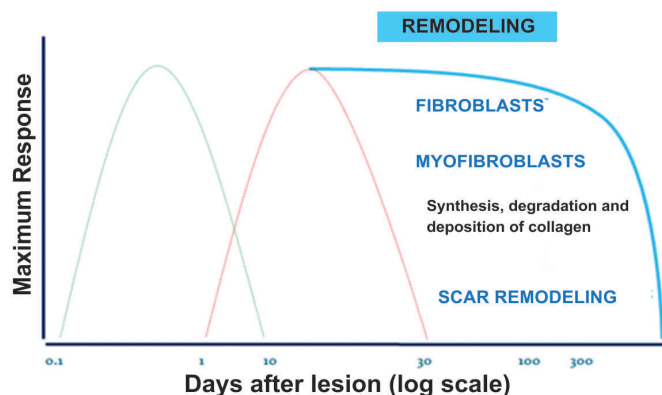
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THE HEALING PROCESS

Classically, trabeculectomy (TREC) is considered the standard surgery for the treatment of glaucoma. However, the surgical success rates in the medium and long term are related to surgical site healing, mainly involving conjunctival and tenonian tissue. The healing process is divided into 4 main phases: coagulative, inflammatory, proliferative, and remodeling (Figure 1), with a series of chemical cascades and biochemical factors released in an attempt to restore hemostasis.⁽¹⁾



Source: Adapted from https://www.iogen.fi/wp-content/uploads/2017/10/ologen-trab-brochure_english-1.pdf

Figure 1: Cell repair process during and after the surgical process.

In the earliest stages, the process is controlled by the immediate release of plasma proteins, blood cells, platelets, and local hormones by initially sealing the injured vessels. With tissue injury, there is the release of histamine, serotonin, and bradykinin causing vasodilation and increased blood flow at the site.⁽²⁾ In the later stages, activated platelets play a key role by releasing chemical growth factors. These substances act as powerful inflammatory chemoattractants, and at the same time the coagulation factors are activated progressing with the first phase of healing.^(3,4)

The microenvironment with its altered physicochemical composition initiates the influx of neutrophils and monocytes (later tissue macrophages), inaugurating the inflammatory phase. Growth factors released from macrophages and cytokines secreted by T-lymphocytes play a very important stimulatory role in the initial phase and regulatory action in the late healing phase.^(5,6)

The proliferative phase begins with the proliferation of epithelial cells in the periphery of the wound concomitant with angiogenesis and fibroplasia (production of collagen by fibroblasts), generating a new tissue matrix. Its main function is to restore the continuity of the damaged tissue, working as a framework for cell migration. The fibroblast is the main protagonist of this process, because in addition to the production of the main constituent of the cell matrix it differs in myofibroblast, which is a more contractile phenotype responsible for the traction of the wound margins.

Over time, this primitive fibrovascular tissue develops into a mature scar in the final stage of healing. The degradation of the extracellular matrix is mediated by plasminogen activators, and the matrix metalloproteinases by the removal of hyaluronic acid and fibronectin from the tissue. Fibroblast apoptosis is an important event in the remodeling phase, causing the wound to

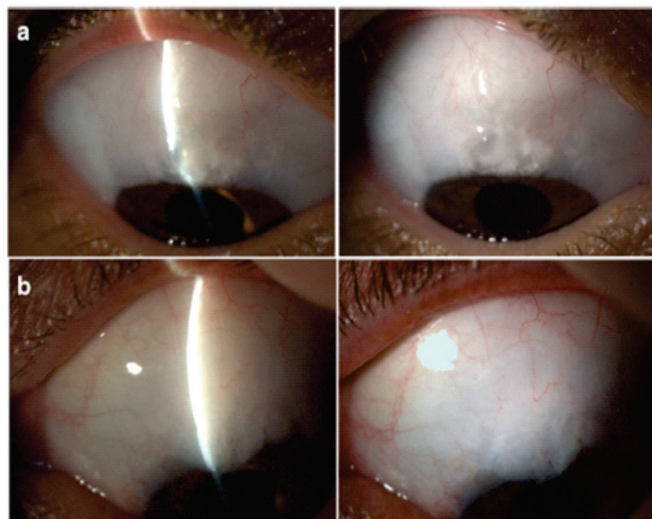
become as close as possible to the initial tissue.^(5,6) Its maturation is characterized by an increase in resistance without an increase in the amount of collagen because there is a balance between production and destruction of the collagen fibers during this period by the action of collagenases. The stages of healing are not mutually exclusive but overlapping in time.⁽⁷⁾

HEALING MODULATORS

Antimetabolite drugs, such as 5-fluorouracil (5 FU) and mitomycin C (MMC), are used to control healing in antiglaucomatous surgeries, especially in Trabeculectomy (Trec) and Non-Penetrating Surgeries (EPNP), in order to prevent the formation of scars and improve the success rate of surgeries. However, these substances are associated with increased complication rates such as blister leakage, hypotonia, choroidal detachment, blebitis, hypotonic maculopathy, and endophthalmitis.⁽⁶⁾

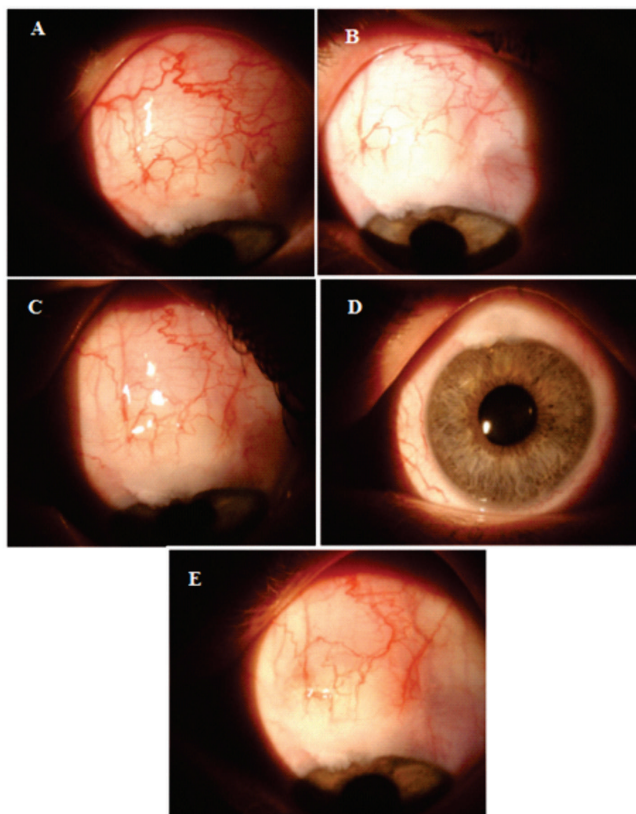
Ologen™ collagen matrix is a new antifibrotic agent comprising a porous matrix of atelocollagen type I and crosslinked glycosaminoglycans which can be used as an alternative for the modulation of healing in surgeries. Because it is highly porous and biodegradable, this implant assists in the physiological repair processes occurring in the connective and epithelial tissues of the lesion without the formation of fibrotic tissue, which leads to surgical failure and elevation of IOP.

It is believed that pores of the collagen matrix ranging in size from 20 to 200 μ m guide randomly proliferating fibroblasts during the remodeling phase. A dynamic physiological reservoir is created to preserve the functionality of the surgery by the formation of a subconjunctival space. The healing process is prevented by the interaction between the tissue and the collagen matrix by optimizing and stabilizing the structure and composition of the ocular tissues, creating a mature fistula, as can be observed in the trabeculectomy surgery (Figures 2 and 3).



Source: Cillino et al. (2016).⁽⁷⁾

Figure 2: (A): A 38-year-old female submitted to TREC with MMC where we observe a diffuse avascular central blister with cystic area; (B): A 52-year-old man of the group TREC with ologen where we observe a diffuse blister with almost normal vascularization.



Source: Anguelov (2013).⁽⁸⁾

Figure 3: TREC postoperative (PO) with OLO implant in left eye. A: 3 days of PO, B: 30 days of PO, C: 5 months of PO, D: 10 months of PO and E: 11 months of PO.

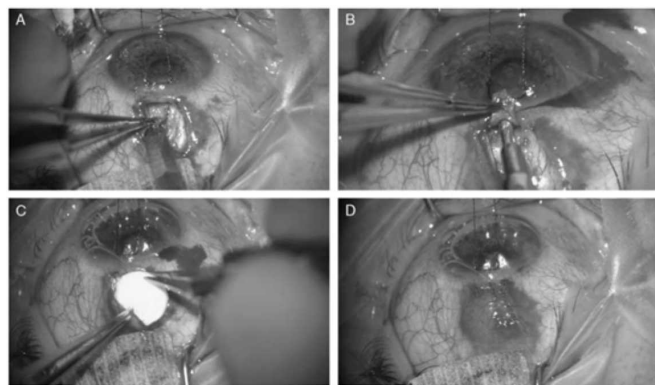
Ologen™ collagen matrix is available in different shapes and sizes (Figure 4). Its biodegradation occurs in a period of 3 to 6 months depending on the conditions of the inflammation and the degree of infiltration.

Shape	Model Number	Size
	830601	6 mm (D) x 2 mm (A)
	830621	7,5 mm (D) x 2 mm (A)
	862051	12 mm (D) x 1 mm (A)
	870051	10 mm (L) x 10 mm (C) x 2 mm (A)

Source: Adapted from <https://www.ologen.com/product/>

Figure 4: Ologen ^TM Collagen Matrix and its models.

Thus, this new implant can be used as an antifibrotic device in different ophthalmologic surgeries, such as TREC (Fig. 5), EPNP, revision of fistulas or drainage implants, in order to create a healthy vascular blister especially in surgeries where the use of antimetabolites is not recommended, as in the elderly, patients with scleral or fine conjunctival tissue, a non-superior blister, history of MMC, and associated complications, among others. (8,9) (Table 1).



Source: Perez et al. (2016).⁽⁹⁾

Figure 5: Trabeculectomy with Ologen implant. A: Trapezoidal scleral flap of 2.5 x 1.5 mm half-thickness made in the upper area. B: Trec was carried out with punch. C: The Ologen implant was positioned over the scleral flap without the use of any sutures. D: The conjunctiva was closed with nylon 10-0.

Table 1
Advantages and Benefits of the Collagen Matrix Ologen™

Characteristics	Advantage	Benefits
Porous structure	Better remodeling in host tissues	Physiological reserve system
90% of atelocollagen type I	Low rejection rate	Minimal immune response
Natural biodegradation	Mimetiza ECM for the regulation of physical consistency	Singular tissue growth
Flexible	Long-term stability of biomechanical tissue	Particular maintenance space
Exceptional dimensions	Ready for use and easy to handle during surgery	Good adaptability to ocular tissue diversity

Source: Translated from <http://www.aeonastron.com/product.php?catId=6>

RESULTS IN THE LITERATURE

Evaluating the safety and efficacy of TREC with Ologen implant versus TREC with MMC, Ji et al.⁽¹⁰⁾ carried out a meta-analysis with 6 randomized clinical trials finding a lower IOP reduction for surgeries with OLOGEN implants compared to MMC surgeries in all the intervals studied, except in the studies followed for more than 24 months. The complications reported were hypotonia with choroidal detachment, seidel, shallow anterior chamber, all with spontaneous resolution, similar in the 2 groups: TREC with Ologen implant and with MMC. There was no significant difference in the reduction of medications for glaucoma and in the success rate when comparing the 2 groups.

In a retrospective study of 24 patients (33 eyes) with POAG, Dada et al.⁽¹¹⁾ evaluated the results of TREC with the use of subconjunctival Ologen combined with low dose of MMC (0.1 mg/ml for 1 min). All eyes reached IOP ≤ 15mmHg, and only in the 6-month visit 2 eyes required hypotensive eye drops. Two eyes with shallow anterior chamber and hypotonia were reported during the

first week, with Seidel suggestive of leakage of conjunctival lesion. There was exposure of the implant in 1 eye after the first week of follow-up. Both were treated with conjunctive resuture. Two other eyes developed a Tenon's cyst at the 8th and 12th postoperative week with elevation of IOP, being treated with infiltrations of 5mg of 5-fluorouracil.

Ologen Collagen Matrix has been used to repair drainage tube exposure as it acts as a tectonic support and biological activities to promote cellular infiltration by the host conjunctival stroma to the surroundings, thus reducing the thinning/erosion of the allogeneic graft.⁽¹²⁾

El-Saied et al.⁽¹³⁾ carried out a prospective, comparative study in 40 eyes of 40 patients with uncontrolled secondary glaucoma followed by failure of TREC with MMC (0.4 mg/ml for 2 min) and three needling attempts with a month interval. Trabeculectomy with Ologen implant was performed 1 month after the last needling. The patients were divided into two groups: Group A comprising 18 eyes of 18 patients with secondary open angle glaucoma, and group B with 22 eyes of 22 patients with secondary closed angle glaucoma. Patients from both groups achieved surgical success with IOP levels ranging from 5 to 18 mmHg. In said study, no intraoperative or postoperative complications were observed, except one eye that developed Dellen.

Dietlein et al.⁽¹⁴⁾ used the Ologen implant in 12 patients who had previously undergone TREC with MMC and were suffering from subsequent ocular hypotonia. They obtained improvement in the IOP levels in the postoperative follow-up. In addition, 9 patients presented improvement in the visual acuity. However, some complications reported in the study were ocular hypotonia, and blister leak with implant exposure 2 weeks after surgery. For resolution, a rotational conjunctival flap was required. Another patient with ocular hypotonia and leakage developed corneal Dellen treated with artificial tears. The cases of choroidal detachment had spontaneous resolution, and 2 patients required hypotensive eye drops at the end of the follow-up period.

In a prospective, comparative study of 16 patients (20 eyes) with congenital glaucoma due to Sturge-Weber syndrome, Mohamed et al.⁽¹⁵⁾ randomized patients into two groups, one group receiving MMC (0.3 mg/ml for 2 min), and another receiving Ologen. An average IOP of 12 mmHg was obtained for those treated with MMC, and 13 mmHg for those treated with Ologen. However, higher levels of postoperative complications were obtained in the MMC group, such as a thin blister with polycysts in 6 eyes, blebitis in 1 eye treated with topical antibiotic, and shallow anterior chamber in 2 eyes, with spontaneous resolution.

Other studies such as Hafez⁽¹⁶⁾ obtained similar results with the use of Ologen in 20 eyes of 15 patients with congenital glaucoma.

CONCLUSION

Os resultados dos atuais estudos com implante de Ologen para o tratamento de glaucoma são encorajadores e promissores. No entanto, ensaios clínicos randomizados futuros com seguimento a longo prazo são necessários para avaliarmos a segurança e a eficácia do novo implante na modulação da cicatrização, alcançando melhores taxas de sucesso cirúrgico.

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