

# Healing modulation in glaucoma surgery after application of subconjunctival triamcinolone acetate alone or combined with mitomycin C: an experimental study

## *Modulação da cicatrização na cirurgia do glaucoma após aplicação de acetato de triancinolona subconjuntival isolado ou em associação à mitomicina C: estudo experimental*

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### ABSTRACT

**Objective:** to study the efficacy and safety of the use of subconjunctival triamcinolone acetate alone or in combination with mitomycin C as a modulator of trabeculectomy healing in rabbits. **Methods:** we submitted thirty male, albino, New Zealand rabbits to bilateral trabeculectomy. We divided the animals into four experimental groups with 15 eyes per group: control, mitomycin C, triamcinolone acetate and triamcinolone acetate + mitomycin C. We performed aplanation tonometry and clinical analysis of the bleb through the Moorfields Graduation System in the postoperative period. For the evaluation of healing, we carried out the quantitative analysis of the inflammatory infiltrate (polymorphonuclear) through Hematoxylin & Eosin staining, and vascular proliferation, through immunohistochemistry. **Results:** we observed a significant decrease in postoperative intraocular pressure in all groups compared with the preoperative pressure ( $p < 0.001$ ). However, there was no difference between groups ( $p = 0.186$ ). The triamcinolone + mitomycin C acetate group presented better indices as for the maximum bleb height and vascularization of the bleb central area ( $p = 0.001$ ); in addition, there was a lower inflammatory response ( $p = 0.001$ ) and lower vascular proliferation ( $p = 0.001$ ) in the intermediate phase of the study compared with the monotherapies. **Conclusion:** the combination of mitomycin C and triamcinolone acetate resulted in a synergistic action between these agents, with broader and more diffuse blebs, less inflammatory infiltrate and less vascular proliferation in the intermediate stages of follow-up in this animal model.

**Keywords:** Glaucoma. Wound Healing. Antimitotic Agents. Trabeculectomy. Ophthalmologic Surgical Procedures.

### INTRODUCTION

Glaucoma is an optic neuropathy that causes irreversible blindness if not treated properly. It is a public health problem, being the second largest cause of blindness in the population<sup>1</sup>. The objective of its treatment is the reduction of intraocular pressure, through topical medications, laser and/or surgical procedures<sup>2,3</sup>. Since the first description, in 1968, trabeculectomy has become the standard procedure in the surgical treatment of glaucoma. It aims at forming a fistula that provides an alternative

route for the drainage of aqueous humor from the anterior chamber to the subconjunctival space, to reduce intraocular pressure (IOP)<sup>3,4</sup>.

Unlike many types of surgery in which complete healing is the desirable outcome, trabeculectomy aims to achieve a partial healing response, to allow continuous drainage of the aqueous humor through the fistula<sup>4</sup>. Modulation of the healing response in glaucoma surgery is often necessary, to achieve adequate pressure, maximizing surgical success<sup>5</sup>. There are a variety of agents available that can modify this response.

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In ophthalmologic practice, antimetabolites, 5-fluorouracil (5-FU) and mitomycin C (MMC), have revolutionized the history of glaucoma surgery and are therefore the drugs most used in modulating healing<sup>4,6</sup>. Although they have enhanced the surgical success rate in trabeculectomy, the non-specific mechanism of these agents may result in various ocular complications, such as corneal toxicity, avascular blebs, endophthalmitis, hypotonia and, in some cases, they are just ineffective<sup>7</sup>. Therefore, there is still a need for alternative strategies to prevent surgical failure secondary to over-healing.

Anti-inflammatory agents are already part of the strategy to modulate inflammation and wound healing in the eye. Steroid hormones are the prototype<sup>4</sup>. Triamcinolone Acetate (TA) is a corticosteroid in the form of an injectable suspension already used for the treatment of neovascular, proliferative and edematous diseases in ophthalmology. Its anti-inflammatory potential is approximately five times that of cortisol<sup>8,9</sup>. The anti-inflammatory and antifibrotic action of TA is largely mediated by suppression of leukocyte concentration and functionality, as well as its effects on vascular permeability. This leads to less local inflammation, reduced release of growth factors, and production of clot and fibrin. As a result, there is a decrease in the fibroblast activity and in the cicatricial response<sup>8,10</sup>.

Although there are already some studies evaluating the use of TA in glaucoma surgery, there is still a need to assess whether TA can be used in monotherapy or only in association with MMC. Therefore, in this research, the objective was to evaluate the efficacy and safety of the use of TA isolated or associated with MMC in trabeculectomy in rabbits.

## **METHODS**

### **Experimental model**

We used thirty male, albino rabbits of the *Oryctolagus cuniculus* species, New Zealand breed, weighing between 2kg and 3kg in the study. The Ethics Committee on Animals of the Federal University of Minas Gerais approved this research, and we treated all animals in accordance with the precepts of the Association for Research in Vision and Ophthalmology (ARVO) - protocol n# CEUA/UFMG 149/2012.

All animals underwent trabeculectomy in both eyes, under sterile conditions, by the same surgeon, using the same technique. General anesthesia was performed with ketamine 35mg/kg + Xylazine 5mg/kg + Acepromazine 0.75mg/kg. We made an upper corneal traction suture with 6-0 silk suture to expose the site to be operated. We prepared a fornix based conjunctival flap and a rectangular scleral flap (3mm x 3mm). Then we proceeded to sclerotomy and peripheral iridectomy. We closed the scleral and the conjunctiva with two 10-0 mononylon sutures. At the end of the procedure, we instilled a drop of 0.5% moxifloxacin and 0.1% dexamethasone.

We distributed the animals in four experimental groups, with 15 eyes per group, since each animal underwent bilateral surgery and received different treatments in the right and left eyes. In the control group, we applied 0.2ml of saline solution through the sponge under the Tenon's capsule and under the scleral flap for two minutes. In the MMC group, we administered 0.4ml of 0.03% mitomycin C via sponge, below the Tenon's capsule and under the scleral flap for two minutes. In the TA group, we

administered 4mg of subconjunctival triamcinolone acetate superior to the bleb at the end of surgery. Finally, in the TA+MMC group, we administered 0.4ml of 0.03% MMC through sponge, below the Tenon's capsule and under scleral flap for two minutes, and, 4mg of subconjunctival triamcinolone acetate superior to the bleb at the end of surgery.

### Clinical analysis

We examined the animals preoperatively and on days one, three, seven, 14 and 30 after the surgical procedure. We performed applanation tonometry using the Perkins Tonometer (Haag-Streit, Koniz, Switzerland) by means of three IOP measurements, recording their mean. We studied the bleb through the photographic evaluation of the surgical site and comparing them with the photos of the Moorfields bleb classification system<sup>11</sup>. Another examiner, unaware of the groups, performed this photographic analysis.

### Immunohistological analysis

With intravenous pentobarbital (150mg/kg), we sacrificed five rabbits from each group and enucleated them on days three, 14 and 30 for evaluation of healing markers. We stained the material with Hematoxylin & Eosin (HE) for all animals and evaluated the region of the operated conjunctiva for polymorphonuclear counts. In the immunohistochemical analysis, we used the VEGF antibody (C-1): SC-7269 (Santa Cruz Biotechnology, California - USA) to investigate the expression of VEGF A in vascular endothelium, evaluating angiogenesis. From each slide, we took three photos in sequence of the area of interest, with a 400-fold increase, which were then evaluated by a pathologist who also did not know the groups.

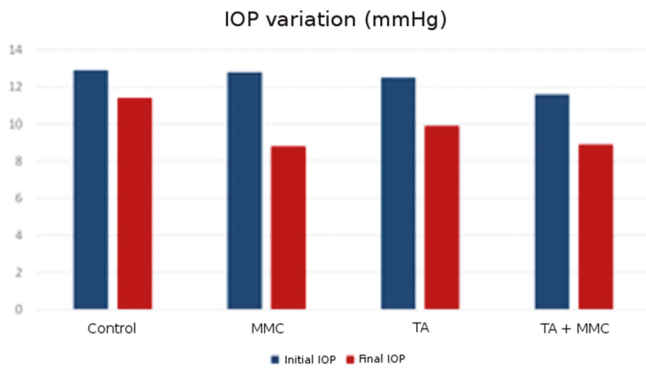
### Statistical analysis

We used the SPSS software, version 19.0. We applied non-parametric tests in the clinical analysis of the bleb. We performed the comparison between independent groups with the Kruskal-Wallis test. In the comparison between the phases, we used the Friedman test. To evaluate the influence of the groups and of the study phases on the intraocular pressure, we used the Variance Analysis based on a Repeated Measures planning. We carried out the evaluation of the influence of the group and the time of evaluation until death of the animals (phase) in the immunohistological variables, as well as the interaction between these two factors (group and phase) using the two-way Analysis of Variance. We considered the results significant for a probability of significance of less than 5% ( $p < 0.05$ ).

## RESULTS

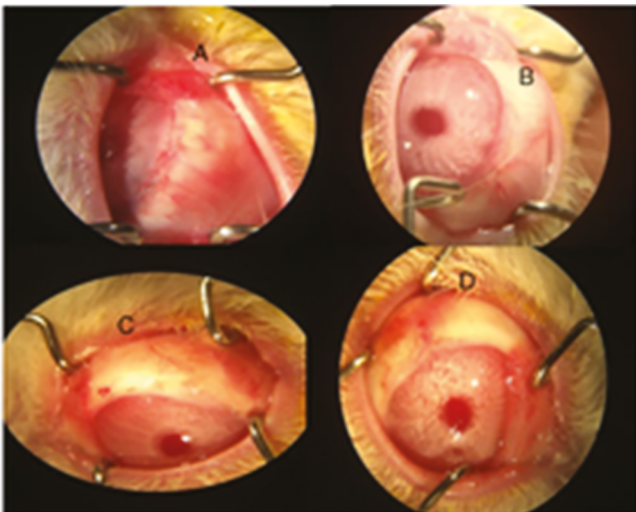
There was no significant difference regarding the animals' initial weight between groups ( $p = 0.910$ ). As for intraocular pressure, in all groups the preoperative values were higher than the values of the final postoperative period ( $p = 0.001$ ). However, there was a significant difference between groups only on the 30th postoperative day (POD): TA+MMC ( $8.9 \pm 0.9$  mmHg) and MMC ( $8.8 \pm 1.5$  mmHg) groups presented the lowest pressure indices, followed by the AT ( $9.9 \pm 1.1$  mmHg) and the control group ( $11.4 \pm 1.5$  mmHg) ( $p = 0.043$ ) (Figure 1).

After the evaluation of the bleb by the Moorfields Bleb Graduation System, in the criteria bleb central area ( $p = 0.002$ ) and maximum area in the 30th POD, there were better results in the TA+MMC ( $2.8 \pm 0.4$ ;  $3.0 \pm 0.0$ ) and MMC ( $2.8 \pm 0.4$ ,



**Figure 1.** Comparison of the initial and final intraocular pressure.

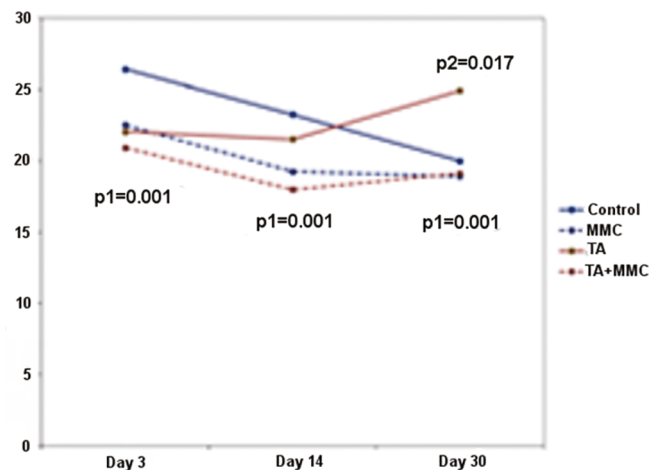
3.0±0.0) groups. In the evaluation of maximum bleb height, the TA+MMC group (1.8±0.4) presented better rates than the other groups (p=0.001). As for the vascularization of the central area, there was a significant difference in the 14th POD, with better results in the TA+MMC group (2.4±0.9; p=0.001). For the vascularization of the maximum bleb area, on its turn, on the 14th POD the lowest indexes were similar in the TA+MMC (2.4±0.5) and MMC (2.4±0.9) groups (p=0.031) (Figure 2).



**Figure 2.** Photographs of the postoperative aspect of trabeculectomy in the seventh POD; Groups: Control (A), MMC (B), TA (C) and TA+MMC (D).

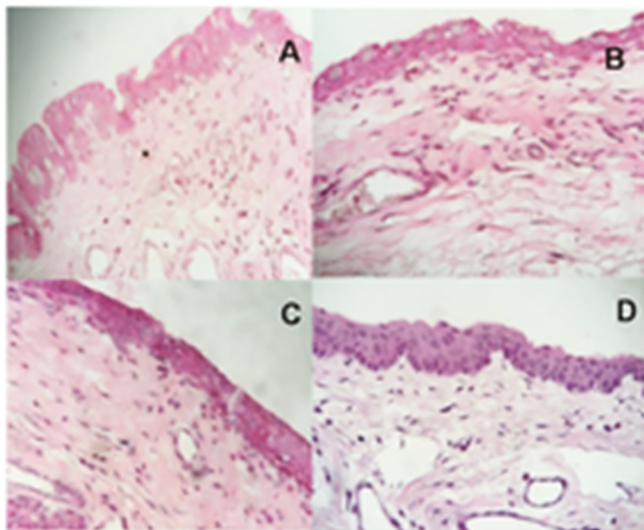
There were few complications during the study, with no significance for the results: two cases of subconjunctival whitish deposit (one case in the TA group and the other in the TA+MMC) that were reabsorbed at the end of the follow-up.

In the quantitative analysis of polymorphonuclear cells throughout the study, the TA+MMC group (20.9±3.7 cells/field) had the lowest cell proliferation, followed by the TA group (22.1±2.3 cells/field; p=0.001). In the intermediate phase, the TA+MMC group (18.0±1.9 cells/field) remained with better results, followed by the MMC group (19.3±2.2 cells/field; p=0.001). At the end of the study, the TA+MMC (19.1±3.1 cells/field) and MMC (18.9±4.5 cells/field) groups presented lower inflammatory infiltrate and the TA group (24.9±4.5 cells/field) had the worst outcome (p=0.001) (Figures 3 and 4).



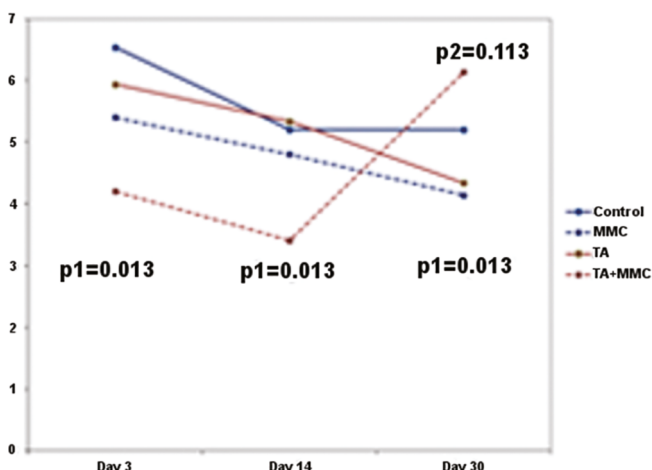
**Figure 3.** Polymorphonuclear count throughout the study; p1: comparison between groups in each phase; p2: comparison in each phase per group.

Angiogenesis, the process of growth of new blood vessels, is a key element of the healing proliferative phase. Its evaluation showed, in the initial phase, better results in the TA+MMC group

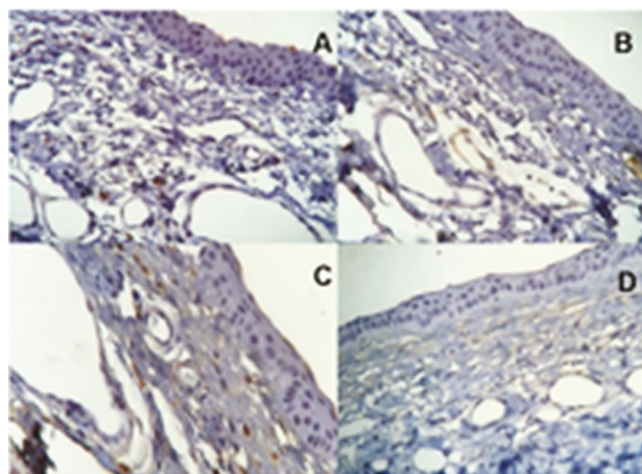


**Figure 4.** Histological sections (HE) of the ocular globe in the conjunctival region of rabbits submitted to experimental surgery, showing the polymorphonuclear count in the 14th POD; Groups: Control (A); MMC (B); TA (C); TA+MMC (D).

( $4.2 \pm 0.9$  vessels marked/field), followed by the MMC group ( $5.4 \pm 1.1$  vessels marked/field) ( $p=0.001$ ). In the 14th POD, the TA+MMC group ( $3.4 \pm 1.0$  labeled vessels/field) remained with the lower rates of vascular proliferation ( $p=0.001$ ). However, at the end of the research, the group with the best results was the MMC one ( $4.1 \pm 1.2$  vessels marked/field) ( $p=0.001$ ) (Figures 5 and 6).



**Figure 5.** Results of vascular proliferation throughout the study; p1: comparison between groups in each phase; p2: comparison in each phase per group.



**Figure 6.** Histological sections (immunohistochemical evaluation) of the conjunctiva of rabbits submitted to experimental surgery, showing the brown chromogen deposition in the vascular endothelium in the 14th POD; Groups: Control (A), MMC (B), TA (C) and TA+MMC (D).

## DISCUSSION

The healing process is a physiological, complex, dynamic event that comprises a cascade of different processes closely linked and not yet fully understood<sup>5</sup>. For long-term success in glaucoma fistulating surgery, complete healing cannot occur. Therefore, the greatest limitation of trabeculectomy is the development of conjunctival and episclera fibrosis secondary to fibroblast proliferation and collagen deposition at the fistula site<sup>12</sup>. In this study, we evaluated the standard modulator, mitomycin C, and an alternative one, triamcinolone acetate, isolated or in combination, in an experimental model of rabbits.

There were lower pressure rates at the end of the study in the TA+MMC and MMC groups, but with no difference between them. However, there was no pressure increase in the groups that used triamcinolone acetate. The use of this anti-inflammatory in ophthalmology is associated with corticosteroid-induced increased intraocular pressure and its subconjunctival injection may cause

this increase for several months. It is believed that this occurs secondarily to the reduction in the ease of flow of the aqueous humor by the trabecular meshwork by deposition of drug particles in the trabecular meshwork<sup>9,13</sup>. The results of the present study are in agreement with the ones of Hogewind *et al.*<sup>8</sup>, who used 20mg of TA in their study, also without pressure increase, suggesting that the effect on the corticoid-induced pressure increase in the trabecular meshwork is compensated by the pressure decrease secondary to trabeculectomy.

The first report of the use of TA as adjuvant in glaucoma surgery was made by Giangiacomo *et al.*<sup>14</sup>, in 1986, who reported 87.5% of surgical success and diffuse blebs at the end of follow-up, suggesting a positive effect of TA on healing modulation. In the present study, when we used TA as monotherapy, it did not demonstrate good results compared with TA+MMC and with isolated MMC, in disagreement with Hogewind, who presented similar surgical success rates between the groups in a five-year follow-up, suggesting that isolated TA could be used as adjuvant in fistulant surgery<sup>8</sup>. This difference in results is justified by the higher dosage used in the study.

Most publications evaluated the use of the TA and MMC association. Tham *et al.*<sup>15</sup>, in a series of cases, injected TA (1.2mg) directly into the filtering ampules of three eyes submitted to facotrabeculectomy, of three undergoing trabeculectomy with MMC, and of five submitted to 5-FU trabeculectomy revision. They reported decreased IOP without the need of medication for up to three months and observed no signs of endothelial loss or progression of cataract. In 2009, another series of cases evaluated the use of retrobulbar TA (20mg) in trabeculectomies with MMC. There was a significant decrease in IOP at six months ( $p < 0.001$ )

without hypotensive medication and there were no complications (infection, hypotonia, conjunctival ulceration)<sup>16</sup>. Although they are only case reports, these results corroborate the positive effect of the association of these modulators on trabeculectomy.

A prospective, randomized, controlled study evaluated the efficacy of subtenonian TA injection (20mg) on the success of trabeculectomies (with MMC) in secondary glaucoma. Complete success was 65.4% in the TA group and 63% in the control group ( $p = 0.77$ ). The fistula characteristics were similar in both groups ( $p > 0.40$ ) and there were no significant differences in the IOP at follow-up ( $p > 0.05$ )<sup>17</sup>. The findings of this study were similar, when TA was associated with MMC in trabeculectomies, to the recent retrospective series of cases that analyzed the administration of intracameral TA (0.1-0.3ml, 4mg/ml). Overall success was 68.4% in the study group and 52.4% in the control group, with partial success being 31.6% and 47.6%, respectively. There was also no increase in complications in the TA group ( $p > 0.05$ )<sup>18</sup>. These results are in agreement with ours, that showed postoperative pressure decrease and good clinical aspect of trabeculectomy in the TA+MMC group, but with similar results to the group using MMC alone.

We have not identified previous studies reporting the effect on the healing cascade of TA and TA+MMC in trabeculectomy in rabbits. In an experimental study that used another corticoid, dexamethasone, in the form of an intravitreal implant, as an adjuvant to trabeculectomy, there was less collagen deposition and longer surgery survival in relation to the control group, but the MMC group presented better results<sup>19</sup>. These findings, in association with the present ones, reinforce the positive action of corticosteroids in the modulation

of wound healing in glaucoma surgery. However, both dexamethasone and triamcinolone acetate were not superior to the standard antifibrotic, MMC. Nonetheless, there was no evaluation of the association of adjuvants, as in the current study, which analyzed the association TA+MMC, showing a greater modulation of healing than these agents isolated in the initial and intermediate phases, both in relation to inflammatory infiltrate and vascular response. This is corroborated by reports that the topical use of corticosteroids postoperatively significantly increases surgical success by inhibiting wound healing as a result of suppression of fibroblast inflammation and proliferation<sup>20</sup>, as well as by screening in humans via culture of Tenon capsule fibroblasts, which showed that corticosteroids inhibit cell binding and proliferation<sup>21</sup>. However, the non-promising results of the isolated TA and the good ones with TA+MMC only up to the intermediate stage in this animal model can be justified by the low dosage of 4mg of this corticosteroid.

This research did not directly evaluate the survival time of the filtering bleb, a criterion used in some experimental studies, defined by a healed, flat and vascularized appearance of the

bleb. Nevertheless, the clinical evaluation using the Moorfields Bleb Graduation System analyzed the extent, height and degree of vascularization at the surgery site, and the poor score of these parameters, indirectly, would point to the survival criterion. Another limitation was the small number of eyes in the final phase of the study, but this number is similar to that of previous publications<sup>12,22</sup>.

Because of the multifactorial nature of wound healing, it is likely that multiple agents, used simultaneously or sequentially, may be required for optimal modulation. The association of MMC with triamcinolone acetate in the current results points to a synergistic action among these agents, with diffuse and broader blebs, less inflammatory infiltrate and less vascular proliferation in the intermediate stage of follow-up in this animal model.

The satisfactory results of the present study, as well as those already published, in relation to the use of TA as adjuvant to trabeculectomies should, however, be considered with caution. Long-term, multicenter, prospective clinical trials are required to assess the optimal dose and route of administration that produce the best surgical outcome with minimal side effects.

## R E S U M O

**Objetivo:** estudar a eficácia e segurança do uso de acetato de triancinolona subconjuntival isolado ou em associação à mitomicina C como modulador da cicatrização de trabeculectomias em coelhos. **Métodos:** trinta coelhos machos, albinos, raça Nova Zelândia foram submetidos à trabeculectomia bilateralmente. Os animais foram divididos em quatro grupos experimentais com 15 olhos por grupo: controle, mitomicina C, acetato de triancinolona e acetato de triancinolona + mitomicina C. Tonometria de aplanção e análise clínica da bolha através do Sistema de Graduação de Moorfields foram obtidas no pós-operatório. Para a avaliação da cicatrização, procedeu-se à análise quantitativa do infiltrado inflamatório (polimorfonucleares) através da coloração Hematoxilina & Eosina e da proliferação vascular por imuno-histoquímica. **Resultados:** foi observada em todos os grupos diminuição significativa da pressão intraocular pós-operatória em relação à pré-operatória ( $p < 0,001$ ). Contudo, não houve diferença entre os grupos ( $p = 0,186$ ). O grupo acetato de triancinolona + mitomicina C apresentou melhores índices na altura máxima da bolha e na vascularização da área central da bolha ( $p = 0,001$ ); além disso, houve menor resposta inflamatória ( $p = 0,001$ ) e menor proliferação vascular ( $p = 0,001$ ) na fase intermediária do estudo em relação às monoterapias. **Conclusão:** a associação da mitomicina C ao acetato de triancinolona resultou numa ação sinérgica entre esses agentes, com bolhas mais amplas e difusas e menor infiltrado inflamatório e menor proliferação vascular em estágio intermediário do acompanhamento neste modelo animal.

**Descritores:** Glaucoma. Cicatrização. Antimitóticos. Trabeculectomia. Procedimentos Cirúrgicos Oftalmológicos.



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