УДК 617.711:617.715]-089-003.93-08-039.71:615.27
https://doi.org: 10.20538/1682-0363-2019-3-46–52

# Pathomorphological features of conjunctival and scleral regeneration associated with intraoperative application of Cyclosporin A

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## ABSTRACT

**Purpose.** In experiment *in vivo* to study the features of regeneration of the conjunctiva and sclera of rats after surgery with intraoperative application of a 0.05% Ciclosporin A.

**Materials and methods.** Experimental animals (rats) ($n$ = 48) were divided into the main group, including the subgroups *a* ($n$ = 16) and *b* ($n$ = 16) and the comparison group ($n$ = 16). Performed a through cut of the conjunctiva and damage to the surface layers of the sclera one of the eyes of all animals. Further on the surgical trauma zone in the main group, the intraoperative application of the cytostatic was performed. In the subgroup *a* with a duration of 3 minutes, in the subgroup *b* – 6 minutes. In the comparison group a hemostatic sponge without a cytostatic was used intraoperatively.

**Results.** In the comparison group postoperative period proceeds with a stereotyped dynamics of cell phase changes in damaged tissues. In the end the development of dense conjunctival-scleral fusion in the area of surgical trauma was noted. Intraoperative application of 0.05% Cyclosporine A leads to a slowing of regeneration, preventing formation of rough conjunctival-scleral scar.

**Conclusions.** Intraoperative applications of 0.05% Cyclosporin A change the stereotyped dynamics of the inflammatory-reparative regeneration in the surgical intervention zone, inhibiting the migration of cells almost in 3 times and significantly (in 2 times) prolonging the duration of the macrophage phase. This causes a slowdown of reparative regeneration, prevents excessive scarring in the operating area.

**Key words:** rat eye bulb, postoperation scarring, cytostatic prophylaxis of abundant regeneration.

**Conflict of interest.** The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

**Source of financing.** The authors state that there is no funding for the study.

**Conformity with the principles of ethics.** The study approved by the local ethics committee under SSMU (Protocol No. 4346 of 16.11.2015).

**For citation:** Zhigalskaya T.A., Krivosheina O.I., Dzyman A.N., Khlusov I.A. Pathomorphological features of conjunctival and scleral regeneration associated with intraoperative application of Cyclosporin A. *Bulletin of Siberian Medicine*. 2019; 18 (3): 46–52. https://doi.org: 10.20538/1682-0363-2019-3-46–52.

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УДК 617.711:617.715]-089-003.93-08-039.71:615.27
https://doi.org: 10.20538/1682-0363-2019-3-46–52

# Патоморфологические особенности регенерации конъюнктивы и склеры на фоне интраоперационной аппликации раствора циклоспорина А

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**РЕЗЮМЕ**

**Цель работы:** в эксперименте *in vivo* изучить особенности регенерации конъюнктивы и склеры крыс после хирургического вмешательства и интраоперационной аппликации 0,05%-го раствора циклоспорина А.

**Материалы и методы.** Экспериментальные животные (самцы крыс, $n = 48$) были разделены на основную группу, включающую подгруппы *a* ($n = 16$) и *b* ($n = 16$), и группу сравнения ($n = 16$). Всем животным выполняли сквозной разрез конъюнктивы и непроникающий надрез поверхностных слоев склеры одного из глаз. На область хирургической травмы в основной группе накладывалась гемостатическая губка, пропитанная 0,05%-м раствором циклоспорина А: в подгруппе *a* длительностью 3 мин, в подгруппе *b* – 6 мин. В группе сравнения интраоперационно накладывалась гемостатическая губка без цитостатика.

**Результаты.** У животных группы сравнения послеоперационный период протекал со стереотипной динамикой смены клеточных фаз в поврежденных тканях. В исходе отмечено развитие плотного конъюнктивально-склерального сращения в зоне хирургической травмы. Интраоперационная аппликация 0,05%-м раствором циклоспорина А приводила к замедлению регенерации, препятствовала формированию грубого конъюнктивально-склерального рубца.

**Заключение.** Интраоперационные аппликации 0,05%-го раствора циклоспорина А меняют стереотипную динамику течения воспалительно-репаративной регенерации в зоне хирургического вмешательства, подавляя практически в три раза миграцию клеток, и значительно (в два раза) увеличивая продолжительность макрофагальной фазы. Это обусловливает замедление репаративной регенерации, препятствующее избыточному рубцеванию в операционной зоне.

**Ключевые слова:** глазное яблоко крыс, послеоперационное рубцевание, цитостатическая профилактика избыточной регенерации.

**Конфликт интересов.** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

**Источник финансирования.** Авторы заявляют об отсутствии финансирования при проведении исследования.

**Соответствие принципам этики.** Исследование одобрено локальным этическим комитетом СибГМУ (протокол № 4346 от 16.11.2015).

**Для цитирования:** Жигальская Т.А., Кривошеина О.И., Дзюман А.Н., Хлусов И.А. Патоморфологические особенности регенерации конъюнктивы и склеры на фоне интраоперационной аппликации раствора циклоспорина А. *Бюллетень сибирской медицины.* 2019; 18 (3): 46–52. https://doi.org: 10.20538/1682-0363-2019-3-46–52.

## INTRODUCTION

Prevention of excessive tissue regeneration in the postoperative period is one of the most urgent problems of medicine. To prevent gross scarring, antimetabolic agents are used, the local application of which significantly reduces the severity of the inflammatory-reparative reaction in the area of surgical intervention and prevents intense fibrogenesis. In ophthalmic surgery, in particular, during anti-glaucoma operations, applications of 5-fluorouracil and mitomycin C are applied to the area of surgically created outflow pathways of the intraocular fluid [1–6]. However, the widespread use of these drugs is limited due to the high risk of complications: inconsistency of sutures, ciliochorioid detachment, cataract progression, and hypotension of the eyeball [7, 8]. In connection with the foregoing, a promising antiproliferative agent may be the intraoperative use of a new generation of cytostatics: - a 0.05% solution of cyclosporin A.

## MATERIALS AND METHODS

The study was performed on the basis of biological models of the Siberian State Medical University. The experiment was performed on 48 male Wistar rats (48 eyes) weighing 200–250 g. All animals underwent a through incision of the sclera conjunctiva and a non-penetrating incision of the surface layers of the sclera in the upper part of the right eyeball in an operating room under general anesthesia . Depending on the course of the operation, the animals were divided into two groups: the main group ($n = 32$) and the comparison group ($n = 16$).

During the operation, the animals of the main group, after an incision through the conjunctiva and non-penetrating incision of the surface layers of the sclera, had a hemostatic sponge soaked in a 0.05% solution of cyclosporin A placed on the intervention zone. The animals of the main group were divided into two subgroups: subgroup *a* ($n = 16$, duration of application was 3 minutes; subgroup *b* (n = 16, duration of application was 6 minutes). In the rats of the control group ($n = 16$), a hemostatic sponge without cyclosporin A solution was applied to the intervention zone for 3 minutes. At the end of the application, the hemostatic sponge was removed in rats of all groups, a Tobrex solution was instilled, and no sutures were applied. In the postoperative period, all animals were instilled with Tobrex solution three times a day in the conjunctival cavity of the operated eye. The total duration of the experiment was 21 days. On the 3rd, 7th, 14th and 21st days after the operation, four animals from each group were removed from the experiment, followed by enucleation.

The euthanizing of experimental animals at all stages of the experiment was carried out in compliance with the rules and norms of the European Society (86 / 609EEC), the Helsinki Declaration and Orders of the USSR Ministry of Health (No. 742 of 13.11.1984 and No. 48 of 23.01.1985). The animals were removed from the experiment by decapitation after general anesthesia. The material was fixed, followed by staining with hematoxylin and eosin and according to the method of Mallory for light microscopy, × 100, × 200. Using a Canon Power Shot G10 digital camera (Japan), 10 random fields of view were taken for each section, using the ImageJ 1.46 program and the Cell Counter plug-in, the absolute and relative content of cells in the conjunctiva and sclera of rat eyes were calculated in the area of operation. Statistical analysis of the results was performed using the statistical package IBM SPSS Statistics 20. The normality of the distribution of indicators was checked using the Kolmogorov – Smirnov law. The results are presented in the form $M \pm m$, where M is the sample mean, and m is the error in mean. Due to the mismatch between the distribution of data and the normal distribution law, the nonparametric Mann-Whitney U-test was used. Differences were considered statistically significant at a significance level of $p < 0.05$.

## RESULTS

According to light microscopy, on the 3rd day after surgery in rats of the subgroup *a* of the main group in the intervention area with the application of a 0.05% solution of cyclosporin A lasting for 3 minutes, diffuse edema was detected in the conjunctiva, and pronounced separation of collagen fibers was revealed in the sclera. Mononuclear leukocytes (MNL) prevailed in the cellular composition in the intervention zone with 846 ± 14.0 (76%) cells in the field of view, the number of polymorphonuclear leukocytes (PML) and fibroblasts was 38 ± 2.0 (3.4%) and 229 ± 9.0 (20.6%), respectively.

In rats of the subgroup *b*, on the 3rd day in the intervention area with the application of a cytostatic solution of 6 min duration, pronounced thinning of the conjunctival epithelium, subepithelial slit cavities, disorientation, and fragmentation of collagen fibers in the sclera were noted. In the cell

composition, MNL prevailed with339 ± 7.0 (80.2%) of the cells in the field of view, the number of PML and fibroblasts was 6.0 ± 1.0 (1.4%) and 78 ± 3.0 (18.4 %), respectively.

In rats of the comparison group, the conjunctival epithelium in the area of the operation was flattened; perivascular edema and a convoluted course of collagen fibers were found in the sclera. Among the cells, MNL prevailed with 795 ± 23.0 (67.8%) of the cells in the field of view, the number of PML was 46 ± 4.0 (3.9%), and fibroblasts was 332 ± 8.0 (28.3%).

On the 7th day in animals of subgroup *a*, a gradual regeneration of the normal architectonics of the conjunctival epithelium began, but the collagen fibers of the sclera were stratified. The cell composition was dominated by MNL with 637 ± 18.0 (57.4%) cells in the field of view. The number of PML increased 2.2 times, up to 82 ± 1.0 (7.4%), $p$ <0.05; the number of fibroblasts was 1.7 times, up to 391 ± 15.0 (35.2%) cells compared with the indicators on the 3rd day, $p$ <0.05.

In rats of the subgroup *b*, thinning of the conjunctival epithelium and subepithelial small gaps were noted in the area of cytostatic application. The orientation and tinctorial properties of the collagen fibers of the sclera were significantly impaired. Among the cells, MNL prevailed with 442 ± 14.0 (66.1%) of the cells in the field of view. The number of PML increased by 4.5 times, to 27 ± 7.0 (4.1%), fibroblasts increased by 2.6 times, to 199 ± 11.0 (29.8%) cells compared with the level at day 3, $p$ <0.05. However, on the 7th day, these parameters in rats of the subgroup *a* were 3.0 and 2.0 times less, respectively, $p$ <0.05.

In rats of the comparison group, on the 7th day, the conjunctival epithelium in the area of operation had a normal structure; the sclera was represented by loose fibrous connective tissue. In the cellular composition, the number of MNL decreased by 1.5 times, to 530 ± 16.0 (46.1%) of the cells in the field of vision compared with the 3rd day, $p$ <0.05. The number of PMLs increased 2.0 times, to 91 ± 11.0 (7.9%), fibroblasts increased by 1.6 times, up to 529 ± 18.0 (46.0%) cells in the field of view compared with the results on the 3rd day, $p$ <0.05.

On the 14th day, in rats of the subgroup *a*, the conjunctiva epithelium had a normal structure in the area of cytostatic application; the collagen fibers of the sclera were loose. Fibroblasts predominated among the cells with 201 ± 13.0 (57.7%) of the cells in the field of view, however, their number compared to the level on the 7th day decreased 2.0 times, $p$ <0.05. The number of MNL decreased by 4.8 times, to 132 ± 12.0 (38%) cells, the number of PML decreased by 5.5 times, to 15 ± 9.0 (4.3%) of cells compared to the 7th day, $p$ <0.05.

In rats of the subgroup *b*, the conjunctival epithelium had a normal structure in the area of cytostatic application; however, small gaps were subepithelially detected. Bundles of collagen fibers of the sclera in the area of operation were loose. Fibroblasts predominated in the cellular composition at 120 ± 12.0 (50%) and MNL at 106 ± 10.0 (44.2%) cells in the field of view, while the number of cells in these populations was less than in rats of the subgroup a by the 14th day was1.7 and 1.3 times less, respectively, $p$ <0.05. The number of PML decreased by 1.9 times compared with the indicator on the 7th day with 14 ± 2.0 (5.8%) cells in the field of view, $p$ <0.05.

In rats of the comparison group, on the 14th day after the operation, the eyeball conjunctiva in the intervention area had a normal structure; thick bundles of collagen fibers of the sclera were denser. The number of fibroblasts decreased 2.2 times, to 241 ± 12.0 (51.9%) of the cells in the field of view, which, however, was 2.0 times higher than this indicator in animals of the subgroup *b* on the 14th day, $p$ < 0.05. The number of PML compared with the level on the 7th day decreased 1.7 times, MNL was 4.2 times less, amounting to 88 ± 3.0 (18.8%) and 136 ± 8.0 (29.3%) cells, respectively, $p$ <0.05.

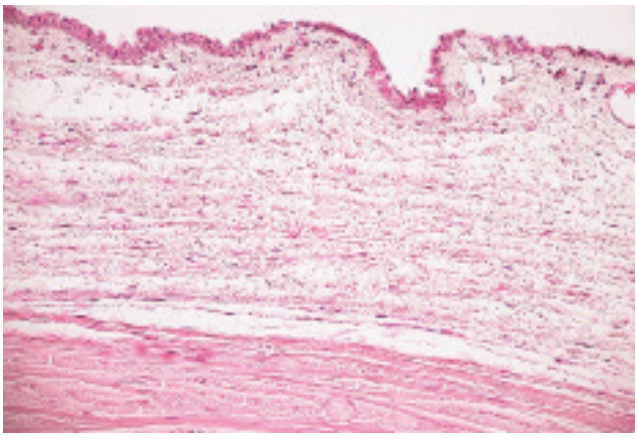

Fig. 1. Condition of the conjunctiva and sclera of the eye in the area of intervention in the experimental animal subgroup *a* of the main group on the 21st day after surgery with a 3-minute application of a 0.05% Cyclosporin A. Color by hematoxylin and eosin, ×200

Рис. 1. Состояние конъюнктивы и склеры глазного яблока в области вмешательства у экспериментального животного подгруппы *а* основной группы на 21-е сут после операции с 3-минутной аппликацией 0,05%-го раствора циклоспорина А. Окраска гематоксилином и эозином, ×200

On the 21st day, the animals of the subgroup *a* in the area of application of the conjunctival cytostatic had a normal structure and tightly adhered to the sclera, but was not adhered to it (Fig. 1).

The course of collagen fibers of the sclera in the area of operation was ordered. Fibroblasts predominated among the cells with 121 ± 12.0 (68.8%) of the cells in the field of view, their number compared to the level on the 14th day decreased 2.0 times, $p < 0.05$. The number of PML decreased by 1.7 times, to 9 ± 1.0 (5.1%), MNL decreased by 1.5 times, to 46 ± 8.0 (26.1%) of cells in the field of view compared with the indicators on the 14th day, $p < 0.05$.

In rats of the subgroup *b* the conjunctiva in the area of application of the cytostatic had a normal structure, however, small cracks remained subepithelial. In this case, the conjunctiva was separated from the sclera by a slit-like space (Fig. 2). Bundles of collagen fibers of the sclera in the area of intervention were stratified. Fibroblasts prevailed in the cellular composition with 105 ± 11.0 (52.2%) cells in the field of view and MNL had 84 ± 7.0 (41.8%) cells. Moreover, the number of fibroblasts was 1.2 times less than in the rats of the subgroup *a* on the 21st day ($p < 0.05$).

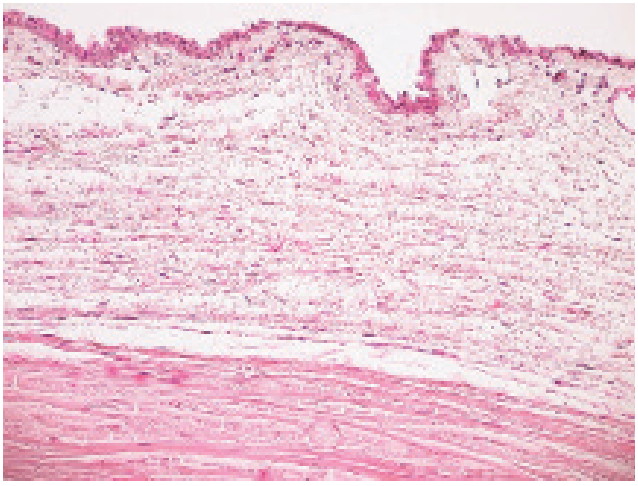

Fig. 2. The slit-like space between the conjunctiva and the sclera in the area of intervention in the experimental animal subgroup *b* of the main group on the 21st day after the operation with 6-minute application of a 0.05% Cyclosporin A. Color by hematoxylin and eosin, ×100

Рис. 2. Щелевидное пространство между конъюнктивой и склерой в области вмешательства у экспериментального животного подгруппы *b* основной группы на 21-е сут после операции с 6-минутной аппликацией 0,05%-го раствора циклоспорина А. Окраска гематоксилином и эозином, ×100

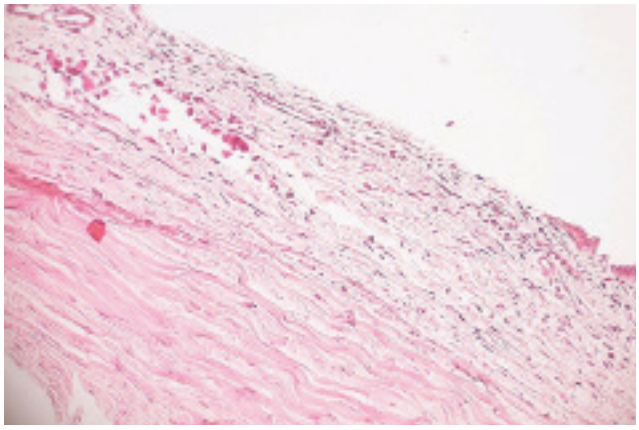

Fig. 3. Conjunctival-scleral scar in the area of intervention in an experimental animal of the comparison group on the 21st day after surgery without local application of a 0.05% solution of Cyclosporin A. Color by hematoxylin and eosin, ×100

Рис. 3. Конъюнктивально-склеральный рубец в области вмешательства у экспериментального животного группы сравнения на 21-е сут после операции без местной аппликации 0,05%-го раствора циклоспорина А. Окраска гематоксилином и эозином, ×100

The number of PML in comparison with the indicator on the 14th day decreased by 1.2 times, to 12 ± 2.0 (6%) cells in the field of view ($p < 0.05$). In rats of the comparison group, on the 21st day after the conjunctiva operation, the eyes in the intervention area had a normal structure, were tightly soldered to the underlying sclera (Fig. 3). The sclera is represented by dense connective tissue. The number of fibroblasts decreased 1.7 times from the level on the 14th day, amounting to 138 ± 12.0 (78.7%) cells in the field of view. However, this was 1.3 times higher than that in rats of the subgroup *b* on the 21st day ($p < 0.05$). The number of PML decreased by 6.3 times compared with the level on the 14th day, MNL decreasedby 5.7 times, amounting to 14 ± 2.0 (7.9%) and 24 ± 5.0 (13.4%) cells, respectively ($p < 0.05$).

## DISCUSSION

The results of the study indicate the development of an inflammatory-reparative reaction in the conjunctiva and sclera after surgery in rats of all experimental groups. In the comparison group, the reaction proceeded with the stereotypic dynamics of the change of cell phases, which reflects its protective and adaptive nature. Throughout the experiment, the cell density in the area of operation in rats of the comparison group was the highest among all experimental groups (Table 1). On the

21st day, the development of dense conjunctival scleral fusion in the intervention area was revealed, which indicates the achievement of the ultimate goal of the inflammatory-reparative reaction: the maximum repair of anatomical tissue.

The use of a 0.05% solution of cyclosporin A in the form of an intraoperative application had a significant effect on the course of the postoperative period, depending on the duration of the application. Apparently, due to the suppression of the synthesis of pro-inflammatory interleukins [9], the cytostatic agent significantly reduced the migration of cells responsible for the intensity of inflammation into the zone of surgical trauma.

On the 3rd day after the operation, the cell density in the intervention area in the subgroup *a* was 1.05 times lower than in the comparison group, however, in the subgroup *b* this indicator was 2.8 times lower ($p < 0.05$) than in the comparison group (see table. 1). A similar dynamics was observed up to 14 days after surgery.

Table

**Dynamics of cell density of infiltrate in a 1 mm² slice in animals of experimental groups, $M \pm m$**

| Terms of observation, days | Experimental groups | | |
|---|---|---|---|
| | Subgroup *a* of the main group | Subgroup *b* of the main group | Comparison group |
| 3 | 6 956 ± 105** | 2 643 ± 115* | 7 328 ± 98,2 |
| 7 | 6 937 ± 98** | 4 175 ± 124* | 7 184 ± 105 |
| 14 | 2 175 ± 95** | 1 500 ± 117* | 2 902 ± 114 |
| 21 | 1 100 ± 97 | 1 256 ± 104 | 1 099 ± 142 |

* statistically significant differences were ($p < 0.05$) when compared with indicators in the group of animals that were operated on without using a local application of a 0.05% Cyclosporin A solution (comparison group).

** statistically significant differences were ($p < 0.05$) when comparing the indicators of the subgroup *a* (Cyclosporin A application 3 minutes) with those of the subgroup *b* (Cyclosporin A application 6 minutes) of the main group.

The intraoperative application of cytostatic solution also influenced the change in the cell phases of the inflammatory-reparative reaction in the tissues in the intervention zone, increasing the duration of the macrophage phase and suppressing the migration of fibroblast population cells to the area of surgical trauma. On the 3rd day after the operation, the fibroblast density in the subgroup *a* was 1.5 times lower ($p < 0.05$), in subgroup b it was 4.3 times lower ($p < 0.05$) than in the comparison group. On the 7th day, the number of fibroblasts in the comparison group increased 1.6 times. In the subgroups *a* and *b*, the shift in the cellular composition of the infiltrate towards the fibroblastic population occurred only on the 14th day after the operation.

## CONCLUSION

The intraoperative application of the 0.05% solution of cyclosporin A during the operation on the conjunctiva and sclera of the rat eyeball in an *in vivo* experiment changes the typical dynamics of the course of the inflammatory-reparative reaction in the intervention area, suppressing cell migration almost three times, and significantly (by two times) increasing the duration of the macrophage phase. This leads to a slowdown in reparative regeneration, which prevents excessive scarring in the operating area. The results obtained may be useful in clinical situations.

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Received 18.04.2019
Accepted 11.06.2019

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Поступила в редакцию 18.04.2019
Подписана в печать 11.06.2019