DOI: https://doi.org/10.17816/OV62857

The platelet-rich plasma lysate use in the treatment of persistent epithelial defects after keratoplasty

© Sergei V. Trufanov[1], Anastasiya M. Subbot[2], Nare P. Shakhbazyan[2]

[1] Pavlov First St. Petersburg State Medical University, Saint Petersburg, Russia;
[2] Research Institute of Eye Diseases, Moscow, Russia

AIM: to evaluate the effectiveness of the platelet-rich plasma lysate (PRP lysate) use in the treatment of persistent epithelial defects (PED) after keratoplasty.

MATERIALS AND METHODS: In the study, 60 patients with PED after keratoplasty were included. The 1st group (24 cases) included patients after keratoplasty with "low risk" of rejection, and the 2nd group – 36 cases after keratoplasty with "high risk" of rejection. Each group was divided into two subgroups – control subgroups 1a (cases 10) and 2a (cases 16), where patients received only standard postoperative therapy, and the main subgroups 1b (cases 14) and 2b (cases 20), in which PRP lysate was prescribed against the background of standard therapy, starting from the Day 15 post-op. As the criterion for effective treatment, complete persistent epithelialization after keratoplasty was considered.

RESULTS: The effectiveness of the use of PRP lysate in the subgroup 1b was 85.7%, while complete epithelialization in the control subgroup 1a was recorded in 70%; in the subgroup 2b, complete epithelialization was observed in 55%, in the control subgroup 2a – in 43.75%.

CONCLUSION: The use of PRP lysate in the treatment of PED after corneal transplantation as an adjuvant therapy is effective and safe in both high and low risk keratoplasty. In the examined category of patients, treatment with blood derivatives increases the frequency and rate of complete epithelialization.

Keywords: epithelial defect; platelet-rich plasma lysate; keratoplasty; corneal epithelium.

To cite this article:
Trufanov SV, Subbot AM, Shakhbazyan NP. The platelet-rich plasma lysate use in the treatment of persistent epithelial defects after keratoplasty. *Ophthalmology Journal*. 2021;14(2):27-35. DOI: https://doi.org/10.17816/OV62857

Received: 18.03.2021 **Accepted:** 14.06.2021 **Published:** 25.06.2021

DOI: https://doi.org/10.17816/OV62857

Применение лизата обогащенной тромбоцитами плазмы в лечении пациентов с персистирующими эпителиальными дефектами после кератопластики

© С.В. Труфанов[1], А.М. Суббот[2], Н.П. Шахбазян[2]

[1] Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова, Санкт-Петербург, Россия;
[2] Научно-исследовательский институт глазных болезней, Москва, Россия

Цель исследования. Оценить эффективность применения лизата обогащенной тромбоцитами плазмы (лизат ОбТП) в лечении пациентов с персистирующими эпителиальными дефектами (ПЭД) после кератопластики.

Материалы и методы. В исследование было включено 60 пациентов с ПЭД после кератопластики: 1-я группа (n = 24) включала больных после кератопластики «низкого риска»; 2-я группа (n = 36) — после кератопластики «высокого риска» отторжения. Каждая группа была разделена на две подгруппы — контрольные 1а (n = 10) и 2а (n = 16), где пациенты получали только стандартную послеоперационную терапию, и основные 1б (n = 14) и 2б (n = 20), где на фоне стандартной терапии начиная с 15-х послеоперационных суток назначали инстилляции глазных капель лизата ОбТП. Критерием эффективного лечения считали полную стойкую эпителизацию после кератопластики.

Результаты исследования. Эффективность применения лизата ОбТП в подгруппе 1б составила 85,7 %, тогда как полная эпителизация в контрольной подгруппе 1а зафиксирована в 70 %; в подгруппе 2б полная эпителизация наблюдалась в 55 %, в контрольной подгруппе 2а — 43,75 %.

Заключение. Применение глазных капель лизата ОбТП в лечении при ПЭД после трансплантации роговицы в качестве адъювантной терапии эффективно и безопасно при кератопластике как высокого, так и низкого риска. У обследуемой категории больных лечение дериватами крови увеличивает частоту и скорость полной эпителизации.

Ключевые слова: эпителиальный дефект; лизат обогащенной тромбоцитами плазмы; кератопластика.

Как цитировать:
Труфанов С.В., Суббот А.М., Шахбазян Н.П. Применение лизата обогащенной тромбоцитами плазмы в лечении пациентов с персистирующими эпителиальными дефектами после кератопластики // Офтальмологические ведомости. 2021. Т. 14. № 2. С. 27–35. DOI: https://doi.org/10.17816/OV62857

Рукопись получена: 18.03.2021 **Рукопись одобрена:** 14.06.2021 **Опубликована:** 25.06.2021

INTRODUCTION

Plasma and platelet-based drugs are successfully used in many branches of medicine for wound healing due to their high content of growth factors. The field of application of such drugs is quite wide; they are used in traumatology and orthopedics, cosmetology, dermatology, sports medicine, cardiac surgery, pediatric surgery, gynecology, urology, plastic surgery, dentistry, and ophthalmology [1–3]. There is currently no standardized protocol for processing whole blood and making eye drops from it. The method of activation, such as collagen, calcium, thrombin, in contact with glass or cycles of freezing and thawing, for producing platelet-based plasma preparations is quite diverse, ranging from a single centrifugation of whole blood in a conventional test tube to specialized commercial systems [4–7]. Chemical activation of platelets is believed to cause side effects, while mechanical lysis by freezing and thawing requires less time, is cost effective, and is biologically safe [8].

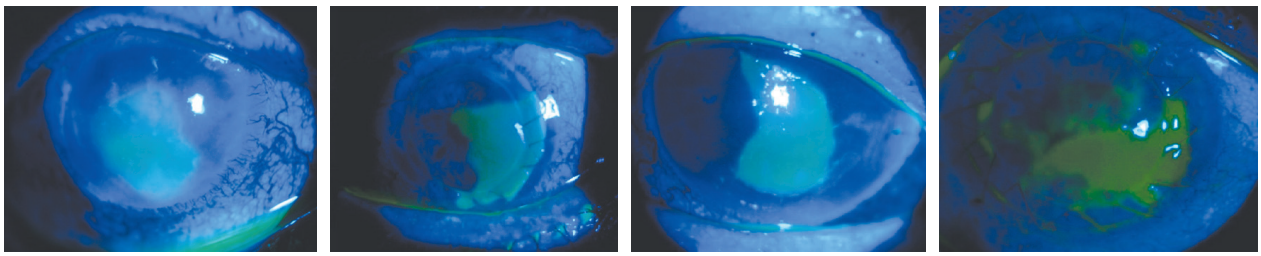
The most popular derivatives of plasma with high platelet content are platelet-rich plasma (PRP), plasma rich in growth factors (PRGF), and PRP lysate. PRP is a preparation of autologous plasma with a platelet concentration that is several times higher than the initial one. PRGF is another autologous PRP obtained from the patient's own blood, which releases a pool of biologically active proteins after activation with calcium chloride [9]. PRP lysate is obtained from PRP by cold shock to induce platelet lysis and release of growth factors [10]. Each of the aforementioned substances represents a biological product, that is, a part of the blood plasma fraction with higher concentration of platelets compared with the whole blood. They are rich not only in platelets, but also in the content of the full spectrum of blood coagulation factors, growth factors, chemokines, cytokines, and other plasma proteins [11]. Studies show that platelets comprise a large number of growth factors and cytokines, which can influence angiogenesis, cell migration, and cell proliferation [12]. Many cytokines secreted by platelets have a direct antimicrobial effect [13, 14], other properties of platelets associated with their anti-inflammatory and analgesic effects have been proven as well [15–17]. It should be noted that platelet concentrates constitute an integral part of intrinsic blood, reducing not only the risk of transmission of blood-borne infections but also the occurrence of immune reactions. Also, the growth factors in these products are not mutagens and do not block the feedback mechanisms of tissue regeneration and repair [18–20]. In the present study, we use PRP lysate eye drops in the treatment of persistent epithelial defects (PEDs) after various types of keratoplasty.

The problem of prolonged re-epithelialization after keratoplasty remains unsolved and urgent. The term PED is commonly used to characterize persistent, non-healing lesions of the corneal epithelium that persist 2 weeks after the standard therapy [21, 22]. Photos of patients with PED during the standard therapy after various types of keratoplasty are presented in Fig. 1.

Autohemotherapy is the most accessible and promising method of treatment, and the use of platelet derivatives is becoming the most attractive point in solving this problem.

MATERIALS AND METHODS

The clinical study was conducted in the Research Institute of Eye Diseases after obtaining approval from the local biomedical ethical committee and informed voluntary consent of the subjects during the period of 2018–2020. A total of 60 patients (60 eyes) with PED following keratoplasty were included in this study. Depending on the degree and depth of the corneal tissue lesion, keratoplasty was performed as subtotal penetrating keratoplasty (SPK), automated anterior lamellar keratoplasty, Descemet's stripping automated endothelial keratoplasty (DSAEK), Descemet's membrane endothelial



a *b* *c* *d*

Fig. 1. Biomicroscopy of the anterior segment with corneal fluorescein staining under focal illumination in blue cobalt light on Day 15 after keratoplasty: *a* – Descemet's stripping automated endothelial keratoplasty; *b* – penetrating keratoplasty; *c* – Descemet's membrane endothelial keratoplasty; *d* – automated anterior lamellar keratoplasty

Рис. 1. Биомикроскопия переднего отрезка глаза с окраской роговицы флюоресцеином при фокальном освещении в синем кобальтовом свете на 15-е сутки после кератопластики: *a* — автоматизированная эндотелиальная кератопластика с удалением десцеметовой мембраны; *b* — субтотальная сквозная кератопластика; *c* — эндотелиальная трансплантация десцеметовой мембраны; *d* — автоматизированная передняя послойная кератопластика

DOI: https://doi.org/10.17816/OV62857

keratoplasty, and re-keratoplasty. Twenty-four patients were women, and 36 were men, aged 45 to 85 years. To assess the effect of PRP lysate eye drops action, subjects were distributed into two groups depending on the etiology of corneal lesions. Group 1 (n = 24) included patients with PED after keratoplasty with low-risk of rejection, group 2 (n = 36) included patients with PED after keratoplasty at high-risk of rejection. Fuchs endothelial dystrophy, pseudophakic bullous keratopathy, as well as other corneal dystrophies, and grades 3 and 4 keratoconus (according to the classification of M. Amsler) were indications for keratoplasty in the group 1. The main indications for performing keratoplasty in the group 2 included vascularized leucoma of various etiologies, opaque engraftment of the graft after keratoplasty. Canned donor material in Borzenk–Moroz medium was used for transplantation. The average shelf life of canned material was 2 ± 1 day.

Depending on the treatment regimen in the postoperative period, each group was divided into two subgroups:

- Controls – 1a (n = 10) and 2a (n = 16), included patients with PED receiving only standard therapy, which included antibacterial (Tobramycin 0.3%, 1 drop q.i.d. for 1 month); anti-inflammatory (Dexamethasone 0.1%, 1 drop 6 times a day, then following a tapering regimen of 1 drop 5 times a day; 1 drop 4 times a day, etc., the duration of therapy depended on the type of surgical intervention); lubricants (Sodium hyaluronate 0.3%, 1 drop 4–6 times a day), reparative (Dexpanthenol 5% t.i.d., drug withdrawal when using a soft contact lens, SCL), and therapeutic SCL (Biotrue, Bausch & Lomb, USA) from the day 15, the SCL was replaced every 2 weeks;
- Main subgroups – 1b (n = 14) and 2b (n = 20), included patients with PED receiving additional treatment along with standard therapy in the form of instillation of eye drops of PRP lysate at a dosage of 1 drop 4–5 times a day, starting from postoperative day 15. Before starting the therapy, voluntary informed consent was obtained from all patients for further treatment.

The course of additional treatment on average ranged from 2 to 6 weeks; in cases of further PED preservation, additional surgical manipulations were used. The most accessible method was biocoating with a dried corneoscleral flap. As criterion for effective treatment, complete persistent epithelialization after keratoplasty was considered. In the absence of complete epithelialization within 12 weeks after surgery in all subgroups and the appearance of signs of initial stromal lysis, despite the ongoing therapy, the continuation of conservative treatment was considered inappropriate. Table 1 presents the distribution of the studied groups evaluated based on the indications for keratoplasty and the method of treatment.

PRP lysate was obtained in the laboratory of fundamental research in ophthalmology of the Research Institute of Eye Diseases.

The following was the method of obtaining PRP lysate. Blood was taken from the cubital vein into a syringe with an anticoagulant (dextrose + sodium citrate) of 1.5 ml, in a volume of 13.5 ml in women and 12.5 ml in men. After the puncture, the sampling was performed smoothly to avoid damaging the blood cells. The blood was then transferred into a test tube (YCELLBIO-KIT, Korea), and a two-stage centrifugation was performed for 5 min at 3500 rpm. Then, the PRP (1.5–2 ml) was extracted in a laminar flow hood, which was subsequently used to prepare the PRP lysate. Thus, the PRP was frozen at a temperature of –80°C, and then slowly thawed at a temperature of 4°C–6°C to release biologically active substances. After thawing, the tube was centrifuged at

Table. Distribution of patients by groups depending on the indications for keratoplasty and the treatment method
Таблица. Распределение пациентов по группам в зависимости от показаний к кератопластике и метода лечения

	Indications for keratoplasty	Subgroup 1a (n = 10)	Subgroup 1b (n = 14)
Low-risk keratoplasty	Fuchs' endothelial dystrophy	7	5
	Pseudophakic bullous keratopathy	3	6
	Degree 3–4 keratoconus	–	2
	Other stromal corneal dystrophies (lattice dystrophy)	–	1
	Indications for keratoplasty	**Subgroup 2a (n = 16)**	**Subgroup 2b (n = 20)**
High-risk keratoplasty	Vascularized leukomata of various etiology	8	14
	Opaque graft retention	8	6
	• after penetrating keratoplasty	5	2
	• after lamellar keratoplasty	3	4

DOI: https://doi.org/10.17816/OV62857

3000 g (relative centrifuge acceleration) for 15 min to precipitate cellular components. In a laminar flow hood, the PRP lysate was processed through a filter with pore diameter of 0.22 μm to remove the remnants of cellular elements, and then transferred into sterile disposable vials, which were given to the patient. The patient kept some of the vials in a freezer at a temperature of –18 °C, and one vial used by the patient was stored at a temperature of 4°C–6°C for no more than 4 days, this storage duration being recommended by A.O. Loshkareva as secure [23]. Further, *pro re nata*, other vials were defrosted at room temperature, and the patient continued to instill their contents over the next 4 days of therapy.

To assess the area of the epithelial defect in the postoperative period, before and after treatment, the cornea was stained with fluorescein (FluoStrips test strips, BIO GLO, India), photoregistered on a TOPCON DC-1 slit lamp (Japan) under focal illumination in blue cobalt light. Analysis of the efficiency of therapy and examination of patients was performed every week from the start of treatment.

RESULTS

PED was found in all patients after keratoplasty receiving standard treatment. When comparing the efficiency of treatment in the group 1, it should be noted that in the absence of additional therapy in the control subgroup 1a (n = 10), the average period of complete epithelialization was 52.3 ± 8.7 days; however, in three patients, complete epithelialization was not achieved, prompting the decision to perform additional surgical interventions to accelerate epithelialization. Patients in subgroup 1b (n = 14) received additional therapy aimed at accelerating epithelialization, starting from the postoperative day 15. In this subgroup, complete epithelialization was noted in 12 patients at an average time of 34.1 ± 3.7 days. The follow-up period after complete persistent epithelialization was 6–18 months; PED recurrence was not registered. In percentage terms, complete epithelialization in subgroup 1a was achieved in 70% of cases, and in 85.7% of cases in subgroup 1b. Group 2 (n = 36) included patients with high-risk keratoplasty, so in subgroup 2a (n = 16), only standard therapy was used, with the mean period of complete epithelialization of 79.5 ± 7 days. Epithelialization was not achieved in nine patients. Complete persistent epithelialization was recorded only in 43.75%. Patients of subgroup 2b (n = 20) received additional treatment along with standard therapy, starting from the postoperative day 15. The average period of complete epithelialization in this group was 44.6 ± 9 days; complete epithelialization was recorded in 11 cases, which corresponds to 55% of effective treatment. In nine patients (45%), the treatment was ineffective, and this required further surgical intervention. The postoperative follow-up period in subgroups was 6–18 months.

Complete epithelialization of the corneal graft during treatment with PRP lysate in subgroup 1b was 85.7%, and in subgroup 2b, the percentage of effective treatment was significantly lower (55%). Comparing the subgroups of patients depending on the management approach, we revealed that the use of PRP lysate reduces the period of complete epithelialization of the corneal graft. Biomicroscopy of the anterior segment revealed a decrease in irritation, hyperemia of the palpebral and bulbar conjunctiva, as well as a decrease in corneal edema compared with patients receiving only standard therapy. A clinical example that confirms the efficiency of the use of plasma products with high platelet content in the treatment of patients with PED after keratoplasty is given below.

Clinical case

Female patient H., 79 years old, was admitted to the Research Institute of Eye Diseases with a diagnosis: "right eye – condition after automated endothelial keratoplasty with Descemet's membrane removal (DSAEK), left eye – Fuchs endothelial dystrophy, both eyes – high myopia, and pseudophakia. On admission, visual acuity of the right eye was 0.5 incorrigible, whereas that of the left eye was 0.01 incorrigible. Intraocular pressure at all stages was within normal limits. Taking into consideration fibrotic changes in the cornea against the background of chronic corneal edema in the left eye, SPK according to the traditional method was performed. In the postoperative period, the patient received standard therapy. On day 15, epithelialization of the graft was absent (Fig. 2). Voluntary informed consent was obtained from the patient for further treatment. Additional therapy was performed against the standard therapy and included daily instillation of eye drops of autologous PRP lysate 4–5 times a day. Complete epithelialization of the graft was recorded on the postoperative day 35 (Fig. 3). The therapy lasted 3 weeks.

Control examinations were performed after 3, 6, 12, 18 months. There was no PED recurrence observed. In 6 months after surgery, visual acuity was 0.25 incorrigible, after 12 months, it was 0.3 with a pinhole aperture.

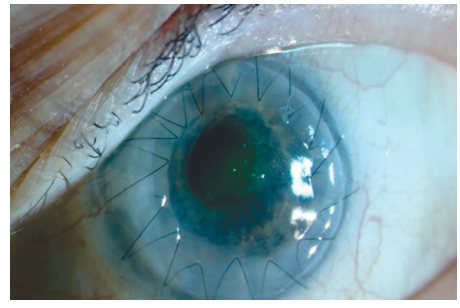


Fig. 2. Before treatment start, Day 15 after surgery
Рис. 2. До начала лечения, 15-е сутки после операции

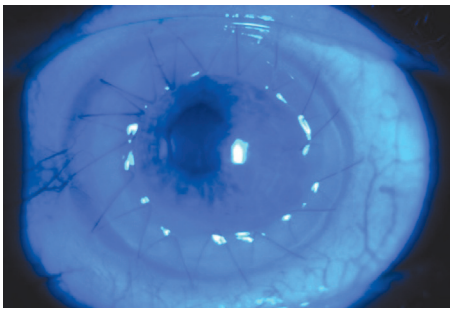


Fig. 3. After treatment with platelet-rich plasma lysate, Day 35 after surgery
Рис. 3. После лечения, 35-е сутки после операции лизатом обогащённой тромбоцитами плазмы

DISCUSSION

Tissue regeneration is a complex and coordinated process involving a number of molecular, cellular, and biochemical mechanisms. Various molecules, growth factors, known for their action on cell adhesion, proliferation and differentiation, are involved in the process of tissue regeneration. PRP lysate provides a combination of many of these, being a key factor in tissue regeneration and wound healing strategies. The advantage of this therapy is the release of autologous growth factors, through which the process of physiological tissue repair is simulated. The data obtained by us in the course of this study confirm the fact of the positive effect of PRP lysate in the treatment of PEDs, while not only the period of complete epithelialization of the graft is reduced, but also its frequency increases in comparison with the control group. However, it should be noted that the effect of therapy is not registered in all cases. There is controversy when comparing our results with those of colleagues from the N.N. Helmholtz National Medical Research Center, where the treatment of PED with blood derivatives was effective in all patients after corneal transplantation [24]. In our study, we obtained positive results in 87.5% and 55% of cases, depending on the degree of keratoplasty risk. In the research by M.A. Abu-Ameerh et al. [25], 4 out of 10 patients had complete epithelialization, three showed partial efficacy, and in three patients, therapy was ineffective, which is more comparable with our results. It is believed that the main causes of failures after keratoplasty include endothelial decompensation, secondary glaucoma, recurrence of the underlying disease, the overlay of infectious complications in the postoperative period, PED of the graft, and corneal suture failure. The most probable causes of PED formation on corneal graft, which can lead to ulceration, local inflammation, vascularization, scar formation, and ultimately to graft opacification, are severe forms of dry eye syndrome, entropion, trichiasis, limbal insufficiency, and tissue incompatibility reaction [26–28]. It should be noted that repeated keratoplasty in patients with opaque engraftment of the graft, due to immune reactions, increases the risk of rejection, which is due to excessive sensitization of the recipient to the corneal tissue of the graft that arose during the previous keratoplasty [29, 30]. In this study, all patients received lubricants; patients with eyelid changes and signs of limbal insufficiency were not included in the study. They also lacked significant typical signs of tissue incompatibility reactions. Nevertheless, in our study, as in similar ones, it is impossible to rule out completely the influence of the immune factor on the delay in epithelialization, especially in the high-risk group. In addition to these factors, it should be taken into account that the rate of epithelialization may depend on the age of the recipient, the size of the graft, the duration of its storage, the type of keratoplasty, and so forth [29, 30]. The study of the efficacy, safety, and tolerability of plasma preparations of platelet derivatives as an alternative treatment for PED after keratoplasty requires further research for its successful implementation in clinical practice.

CONCLUSION

The use of PRP lysate in the treatment of patients with PEDs after corneal transplantation as an adjuvant therapy is effective and safe for both high and low-risk keratoplasty. In the examined category of patients, treatment with blood derivatives increases the frequency and rate of complete epithelialization. Despite the small volume of clinical material, the study did not reveal any complications or side effects when using the above-described therapy.

REFERENCES

1. Lynch MD, Bashir S. Applications of platelet-rich plasma in dermatology: A critical appraisal of the literature. *Journal of Dermatological Treatment.* 2016;27(3):285–289. DOI: 10.3109/09546634.2015.1094178
2. Andia E, Rubio-Azpeitia J, Martin JI, Abate M. Current concepts and translational uses of platelet rich plasma biotechnology. *Biotechnology, Deniz Ekinci, IntechOpen.* 2015. DOI: 10.5772/59954
3. Sommeling CE, Heyneman A, Hoeksema H, et al. The use of platelet-rich plasma in plastic surgery: a systematic review. *J Plast Reconstr Aesthet Surg.* 2013;66(3):301–311. DOI: 10.1016/j.bjps.2012.11.009
4. Mazzucco L, Balbo V, Cattana E, et al. Not every PRP-gel is born equal. Evaluation of growth factor availability for tissues through four PRP-gel preparations: Fibrinet, Regen PRP-kit, Plateltex and one manual procedure. *Vox Sang.* 2009;97(2):110–118. DOI: 10.1111/j.1423-0410.2009.01188. x

5. Le G, Kaux JF, Seidel L, et al. Étude comparative de cinq techniques de préparation plaquettaire (platelet-rich plasma). *Pathol Biol. (Paris)*. 2011;59(3):157–160. (In French.) DOI: 10.1016/j.patbio.2009.04.007

6. Castillo TN, Pouliot MA, Kim HJ, Dragoo JL. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. *Am J Sports Med*. 2010;39(2): 266–271. DOI: 10.1177/0363546510387517

7. Wasterlain AS, Braun HJ, Dragoo JL. *Contents and formulations of platelet rich plasma*. Platelet Rich Plasma in Musculoskeletal Practice. London; 2016. P. 1–29.

8. Bieback K. Platelet lysate as replacement for fetal bovine serum in mesenchymal stromal cell cultures. *Transfus Med Hemother*. 2013;40(5):326–335. DOI: 10.1159/000354061

9. Anitua E, Sanchez M, Merayo-Lloves J, et al. Plasma rich in growth factors (PRGF-Endoret) stimulates proliferation and migration of primary keratocytes and conjunctival fibroblasts and inhibits and reverts TGF induced myodifferentiation. *Investigative ophthalmology visual science.* 2011;52(9):6066–6073. DOI: 10.1167/iovs.11-7302

10. Abu-Ameerh MA, Jafar HD, Hasan MH, et al. Platelet lysate promotes re-epithelialization of persistent epithelial defects a pilot study. *Int Ophthalmology*. 2019;39(7):1483–1490. DOI: 10.1007/s10792-018-0968-1

11. Santos S, Sigurjonsson ÓE, Custódio CA, Mano J. Blood Plasma Derivatives for Tissue Engineering and Regenerative Medicine Therapies. *Tissue Eng Part B Rev.* 2018;24(6):454–462. DOI: 10.1089/ten.TEB.2018.0008

12. Amable PR, Carias RB, Teixeira MV, et al. Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. *Stem Cell Res Ther*. 2013;4(3):67. DOI: 10.1186/scrt218

13. Drago L, Bortolin M, Vassena C, et al. Antimicrobial activity of pure platelet-rich plasma against microorganisms isolated from oral cavity. *BMC Microbiol*. 2013;13:47. DOI: 10.1186/1471-2180-13-47

14. Del Fabbro M, Ceresoli V, Lolato A, Taschieri S. Effect of platelet concentrate on quality of life after periradicular surgery: a randomized clinical study. *J Endod*. 2012;38(6):733–739. DOI: 10.1016/j.joen.2012.02.022

15. van Osch GJ, Bernsen MR, van Buul GM, et al. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. *Am J Sports Med*. 2011;39(11):2362–2370. DOI: 10.1177/036354651141927

16. Mazzocca AD, McCarthy BR, Intravia J, et al. An in vitro evaluation of the anti-inflammatory effects of platelet-rich plasma, ketorolac, and methylprednisolone. *Arthroscopy*. 2013;29(4):675–683. DOI: 10.1016/j.arthro.2012.12.005

17. Peerbooms JC, Sluimer J, Bruijn DJ, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: Platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. *Am J Sports Med*. 2010;38(2):255–262. DOI: 10.1177/0363546509355445

18. Deikalo VP, Mastykov AN, Boloboshko KB. Obogashhennaja trombocitami plazma v lechenii zabolevanij i povrezhdenij oporno-dvigatel'nogo apparata. *Vestnik VGMU.* 2011;10(4):6–12. (In Russ.)

19. Marx RE. Platelet-rich plasma: evidence to support its use. *J Oral Maxillofac Surg*. 2004;62(4):489–496. DOI: 10.1016/j.joms.2003.12.003

20. Huang CJ, Sun YC, Christopher K, et al. Comparison of corneal epitheliotrophic capacities among human platelet lysates and other blood derivatives. *PloS one*. 2018;12(2): e0171008. DOI: 10.1371/journal.pone.0171008

21. McCulley JP, Horowitz B, Husseini ZM, Horowitz M. Topical fibronectin therapy of persistent corneal epithelial defects. Fibronectin Study Group. *Trans Am Ophthalmol Soc*. 1993;91:367–386.

22. Fu Y, Liu J, Tseng SC. Ocular surface deficits contributing to persistent epithelial defect after penetrating keratoplasty. *Cornea*. 2012;31(7):723–729. DOI: 10.1097/ICO.0b013e31821142ee

23. Loshkareva AO. Terapija hronicheskih narushenij jepitelizacii rogovicy gerpesvirusnoj jetiologii s ispol'zovaniem autologichnoj bogatoj trombocitami plazmy [dissertation]. Moscow; 2018. (In Russ.) Available from: https://www.dissercat.com/content/terapiya-khronicheskikh-narushenii-epitelizatsii-rogovitsy-gerpesvirusnoi-etiologii-s-ispolz

24. Borovkova NV, Filatova IA, Chentsova EV, et al. Efficacy of platelet-rich plasma lysate in patients with corneal erosion or post-traumatic scarring of the tissues of the eyelids. *Russian Ophthalmological Journal*. 2020;13(3):8–14. (In Russ.) DOI: 10.21516/2072-0076-2020-13-3-8-14.

25. Rumelt S, Bersudsky V, Blum-Hareuveni T, Rehany U. Preexisting and postoperative glaucoma in repeated corneal transplantation. *Cornea*. 2002;21(8):759–765. DOI: 10.1097/00003226-200211000-00005

26. Rumelt S, Bersudsky V, Blum-Hareuveni T, et al. Preexisting and postoperative glaucoma in repeated corneal transplantation. *Cornea.* 2002;21(8):759–765. DOI: 10.1097/00003226-200211000-00005

27. Puchkovskaja NA. Lechebnaja keratoplastika i vozmozhnosti stimuljacii regenerativnoj sposobnosti rogovoj obolochki. *Oftal'mologichcheskij zhurnal*. 1983;2:69–71. (In Russ.)

28. Katzman LR, Jeng BH. Management strategies for persistent epithelial defects of the cornea. *Saudi J Ophthalmol*. 2014;28(3): 168–172. DOI: 10.1016/j.sjopt.2014.06.011

29. Hos D, Matthaei M, Bock F, et al. Immune reactions after modern lamellar (DALK, DSAEK, DMEK) versus conventional penetrating corneal transplantation. *Prog Retin Eye Res.* 2019;73:100768. DOI: 10.1016/j.preteyeres.2019.07.001

30. Trufanov SV, Subbot AM, Malozhen SA, et al. Risk factors, clinical presentations, prevention, and treatment of corneal graft rejection. *Vestnik oftal'mologii*. 2016;132(6):108–116. (In Russ.) DOI: 10.17116/oftalma20161326108-116

СПИСОК ЛИТЕРАТУРЫ

1. Lynch M.D., Bashir S. Applications of platelet-rich plasma in dermatology: A critical appraisal of the literature // Journal of Dermatological Treatment. 2016. Vol. 27, No. 3. P. 285–289. DOI: 10.3109/09546634.2015.1094178

2. Andia E., Rubio-Azpeitia J., Martin J.I., Abate M. Current concepts and translational uses of platelet rich plasma biotechnology. Biotechnology, Deniz Ekinci, IntechOpen. 2015. DOI: 10.5772/59954.

3. Sommeling C.E., Heyneman A., Hoeksema H., et al. The use of platelet-rich plasma in plastic surgery: a systematic review // J Plast Reconstr Aesthet Surg. 2013. Vol. 66, No. 3. P. 301–311. DOI: 10.1016/j.bjps.2012.11.009

4. Mazzucco L., Balbo V., Cattana E., et al. Not every PRP-gel is born equal. Evaluation of growth factor availability for tissues through four PRP-gel preparations: Fibrinet, Regen PRP-kit, Plateltex and one manual procedure // Vox Sang. 2009. Vol. 97, No. 2. P. 110–118. DOI: 10.1111/j.1423–0410.2009.01188.x

5. Le G., Kaux J.F., Seidel L., et al. Étude comparative de cinq techniques de préparation plaquettaire (platelet-rich plasma) // Pathol Biol. 2011;59:157–160. DOI: 10.1016/j.patbio.2009.04.007

6. Castillo T.N., Pouliot M.A., Kim H.J., Dragoo J.L. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation system // Am J Sports Med. 2010. Vol. 39, No. 2. P. 266–271. DOI: 10.1177/0363546510387517

7. Wasterlain A.S., Braun H.J., Dragoo J.L. Contents and formulations of platelet rich plasma. Platelet Rich Plasma in Musculoskeletal Practice. London. 2016. P. 1–29.

8. Bieback K. Platelet lysate as replacement for fetal bovine serum in mesenchymal stromal cell cultures // Transfus Med Hemother. 2013. Vol. 40, No. 5. P. 326–335. DOI: 10.1159/000354061

9. Anitua E., Sanchez M., Merayo-Lloves J., et al. Plasma rich in growth factors (PRGF-Endoret) stimulates proliferation and migration of primary keratocytes and conjunctival fibroblasts and inhibits and reverts TGF induced myodifferentiation // Investigative ophthalmology visual science. 2011. Vol. 52, No. 9. P. 6066–6073. DOI: 10.1167/iovs.11–7302

10. Abu-Ameerh M.A., Jafar H.D., Hasan M.H., et al. Platelet lysate promotes re-epithelialization of persistent epithelial defects a pilot study // Int Ophthalmology. 2019. Vol. 39, No. 7. P. 1483–1490. DOI: 10.1007/s10792-018-0968-1

11. Santos S., Sigurjonsson Ó.E., Custódio C.A., Mano J. Blood Plasma Derivatives for Tissue Engineering and Regenerative Medicine Therapies // Tissue Eng Part B Rev. 2018. Vol. 24, No. 6. P. 454–462. DOI: 10.1089/ten.TEB.2018.0008

12. Amable P.R., Carias R.B., Teixeira M.V., et al. Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors // Stem Cell Res Ther. 2013. Vol. 4, No. 3. P. 67. DOI: 10.1186/scrt218

13. Drago L., Bortolin M., Vassena C., et al. Antimicrobial activity of pure platelet-rich plasma against microorganisms isolated from oral cavity // BMC microbiol. 2013. Vol. 13. P. 47. DOI: 10.1186/1471-2180-13-47

14. Del Fabbro M., Ceresoli V., Lolato A., Taschieri S. Effect of platelet concentrate on quality of life after periradicular surgery: a randomized clinical study // J Endod. 2012. Vol. 38, No. 6. P. 733–739. DOI: 10.1016/j.joen.2012.02.022

15. van Osch G.J., Bernsen M.R., van Buul G.M., et al. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes // Am J Sports Med. 2011. Vol. 39, No. 11. P. 2362–2370. DOI: 10.1177/036354651141927

16. Mazzocca A.D., McCarthy B.R., Intravia J., et al. An in vitro evaluation of the anti-inflammatory effects of platelet-rich plasma, ketorolac, and methylprednisolone // Arthroscopy. 2013. Vol. 29, No. 4. P. 675–683. DOI: 10.1016/j.arthro.2012.12.005

17. Peerbooms J.C., Sluimer J., Bruijn D.J., Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: Platelet-rich plasma versus corticosteroid injection with a 1-year follow-up // Am J Sports Med. 2010. Vol. 38, No. 2. P. 255–262. DOI: 10.1177/0363546509355445

18. Деикало В.П., Мастыков А.Н., Болобошко К.Б. Обогащенная тромбоцитами плазма в лечении заболеваний и повреждений опорно-двигательного аппарата // Вестник ВГМУ. 2011. Т. 10, No 4. С. 6–12.

19. Marx R.E. Platelet-rich plasma: evidence to support its use // J Oral Maxillofac Surg. 2004. Vol. 62, No. 4. P. 489–496. DOI: 10.1016/j.joms.2003.12.003

20. Huang C.J., Sun Y.C., Christopher K., et al. Comparison of corneal epitheliotrophic capacities among human platelet lysates and other blood derivatives // PloS One. 2018. Vol. 12, No. 2. P. e0171008. DOI: 10.1371/journal.pone.0171008

21. McCulley J.P., Horowitz B., Husseini Z.M., Horowitz M. Topical fibronectin therapy of persistent corneal epithelial defects. Fibronectin Study Group // Trans Am Ophthalmol Soc. 1993. Vol. 91. P. 367–386

22. Fu Y., Liu J., Tseng S.C. Ocular surface deficits contributing to persistent epithelial defect after penetrating keratoplasty // Cornea. 2012. Vol. 31, No. 7. P. 723–729. DOI: 10.1097/ICO.0b013e31821142ee

23. Лошкарева А.О. Терапия хронических нарушений эпителизации роговицы герпесвирусной этиологии с использованием аутологичной богатой тромбоцитами плазмы: дис. ... канд. мед. наук. М., 2018. Режим доступа: https://www.dissercat.com/content/terapiya-khronicheskikh-narushenii-epitelizatsii-rogovitsy-gerpesvirusnoi-etiologii-s-ispolz. Дата обращения: 02.07.2021.

24. Боровкова Н.В., Филатова И.А., Ченцова Е.В., и др. Эффективность применения лизата богатой тромбоцитами плазмы (БоТП) у пациентов с эрозией роговицы или посттравматическим рубцеванием тканей век // Российский офтальмологический журнал. 2020. Т. 13, № 3. С. 8–14. DOI: 10.21516/2072-0076-2020-13-3-8-14

25. Rumelt S., Bersudsky V., Blum-Hareuveni T., Rehany U. Preexisting and postoperative glaucoma in repeated corneal transplantation. Cornea. 2002. Vol. 21, No. 8. P. 759–765. DOI: 10.1097/00003226-200211000-00005

26. Rumelt S., Bersudsky V., Blum-Hareuveni T., et al. Preexisting and postoperative glaucoma in repeated corneal transplantation // Cornea. 2002. Vol. 21. No. 8. P. 759–765. DOI: 10.1097/00003226-200211000-00005

27. Пучковская, Н.А. Лечебная кератопластика и возможности стимуляции регенеративной способности роговой оболочки // Офтальмологический журнал. 1983. № 2. С. 69–71.

28. Katzman L.R., Jeng B.H. Management strategies for persistent epithelial defects of the cornea // Saudi J Ophthalmol. 2014. Vol. 28, No. 3. P. 168–172. DOI: 10.1016/j.sjopt.2014.06.011

29. Hos D., Matthaei M., Bock F., et al. Immune reactions after modern lamellar (DALK, DSAEK, DMEK) versus conventional penetrating corneal transplantation // Prog Retin Eye Res. 2019. Vol. 73. P. 100768. DOI: 10.1016/j.preteyeres.2019.07.001

30. Труфанов С.В., Суббот А.М., Маложен С.А., и др. Факторы риска, клинические проявления, методы профилактики и лечения реакции отторжения трансплантата роговицы // Вестник офтальмологии. 2016. Т. 132, № 6. С. 108–116. DOI: 10.17116/oftalma20161326108-116

AUTHORS' INFO

***Nare P. Shakhbazyan,** postgraduate student;
address: 11A, Roccolimo str., Moscow, 119021, Russia;
ORCID: https://orcid.org/0000-0002-1857-6425;
e-mail: nare_shakhbazyan@mail.ru.

Sergei V. Trufanov, MD, Dr. Sci. (Med.);
ORCID: https://orcid.org/ 0000-0003-4360-793X;
e-mail: trufanov05@mail.ru.

Anastasiya M. Subbot, PhD, Cand. Sci. (Med.);
ORCID: https://orcid.org/ 0000-0002-8258-6011;
e-mail: kletkagb@gmail.com

ОБ АВТОРАХ

***Наре Петросовна Шахбазян,** аспирантка;
адрес: Россия, 119021, Москва, ул. Россолимо, д. 11 А;
ORCID: https://orcid.org/0000-0002-1857-6425;
e-mail: nare_shakhbazyan@mail.ru

Сергей Владимирович Труфанов, д-р мед. наук;
ORCID: https://orcid.org/ 0000-0003-4360-793X;
e-mail: trufanov05@mail.ru

Анастасия Михайловна Суббот, канд. мед. наук;
ORCID: https://orcid.org/ 0000-0002-8258-6011;
e-mail: kletkagb@gmail.com