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EXPERIENCE IN PERSONALIZED CELL THERAPY CLINICAL IMPLEMENTATION FOR TREATMENT OF PATIENTS WITH PRIMARY ENDOTHELIAL DYSTROPHY AFTER PHACOEMULSIFICATION

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✧ The article presents treatment results of the personalized cell therapy (PCT) method in patients with early post-operative bullous keratopathy which developed in eyes with pre-existing primary Fuchs' corneal endothelial dystrophy (ED). The patented PCT consists in incubating *in vitro* the patient's blood with the stimulator (polyA:polyU), collecting serum with activated leukocytes weighted in it, and introducing the obtained cell preparation in the anterior chamber of the patient's eye. The study included 12 patients with ED and pseudophakia. The observation period ranged from 8 to 12 months. The therapeutic effect of PCT was obtained in 58.3% of cases, allowing to avoid further surgical procedures. To achieve a good therapeutic effect, several PCT sessions are recommended. To date, PCT is the only effective therapeutic treatment method for early corneal edema after phacoemulsification.

✧ ***Keywords:*** cornea; epithelial and endothelial dystrophy; corneal endothelial cells; Fuchs' endothelial corneal dystrophy; confocal microscopy; cell therapy; bullous keratopathy.

ОПЫТ КЛИНИЧЕСКОГО ПРИМЕНЕНИЯ ПЕРСОНАЛИЗИРОВАННОЙ КЛЕТОЧНОЙ ТЕРАПИИ ДЛЯ ЛЕЧЕНИЯ БОЛЬНЫХ С ПЕРВИЧНОЙ ЭНДОТЕЛИАЛЬНОЙ ДИСТРОФИЕЙ ПОСЛЕ ФАКОЭМУЛЬСИФИКАЦИИ

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✧ В статье представлены результаты лечения больных с ранней послеоперационной буллёзной кератопатией, развившейся на глазах с предсуществующей первичной эндотелиальной дистрофией роговицы (ЭД) Фукса с помощью методики персонализированной клеточной терапии (ПКТ). Запатентованный

метод ПКТ заключается в инкубации *in vitro* крови пациента со стимулятором (полиА : полиУ), сборе сыворотки со взвешенными в ней активированными лейкоцитами и введении полученного клеточного препарата в переднюю камеру глаза пациента. В работу вошли 12 пациентов с ЭД и артифакией. Срок наблюдения составил от 8 до 12 месяцев. Терапевтический эффект ПКТ был зафиксирован в 58,3 % случаев, что позволило избежать дальнейших хирургических вмешательств. Рекомендуется проведение нескольких сеансов ПКТ для достижения хорошего терапевтического эффекта. ПКТ является единственным эффективным на сегодняшний день методом терапевтического лечения ранних отёков роговицы после факоэмульсификации.

✧ ***Ключевые слова:*** роговица; эндотелиальная дистрофия (ЭД); эндотелиальные клетки; дистрофия роговицы Фукса; конфокальная микроскопия; клеточная терапия; буллёзная кератопатия.

INTRODUCTION

The treatment of corneal disorders is currently one of the most significant challenges in ophthalmology. According to reports of the World Health Organization, corneal disorders are the third most common cause of blindness [3]. Every fifth patient who seeks ophthalmic care develops degenerative, inflammatory, or traumatic lesions of the cornea [5, 10]. An increasing incidence of Fuchs endothelial corneal dystrophy (FECD), which often develops following intraocular surgeries such as phacoemulsification (PE), has also been observed. These patients usually require surgical treatment with keratoplasty. FECD is one of the most common indications (up to 25% of all indications) for keratoplasty in the United States and Europe [9, 11–14]. This procedure is associated with a high risk of transplant rejection and other complications, and some patients may even require repeated surgery. It has been clarified that pharmacotherapy is often ineffective for corneal dystrophy and does not restore corneal transparency. Therefore, the search for new drugs and methods to stimulate metabolism and proliferation in the corneal endothelium remains relevant.

Since the early 2000s, a group of researchers (A.A. Kasparov, E.A. Kasparova, and A.S. Pavliuk) at the Research Institute of Eye Diseases has been successfully using personalized cell therapy (PCT) for treating early (arising at 1–3 months after surgery) postoperative bullous keratopathy [1, 2, 4–8]. The method is protected by the following two patents: "Method for treating postinflammatory bullous keratopathy (No 2165747)" and "Novel medication for treating corneal edema and other manifestations of early bullous keratopathy: technology of its production and administration (No 2357743)." This medical technology was registered in 2013 (protocol No 4 dated 03.06.2013) and approved by the Ethics Committee of the Research Institute of Eye Diseases. The Department of Ophthalmology is authorized to use PCT; the method was also approved by the Ethics Committee of the Pavlov First Saint Petersburg State Medical University (April 2016).

PCT involves the *in vitro* activation of autologous leukocytes from the peripheral blood through successive injections of Poludanum (a complex of polyadenylic acid and polyuridylic acid that acts as an immunomodulator) into the anterior chamber. Poludanum is the only immunomodulatory drug approved for intraocular administration. PCT stimulates the local production of cytokines, including interferon (IFN)-α, IFN-β, IFN-γ, interleukin (IL)-2, IL-6, IL-8, and tumor necrosis factor (TNF)-α. Together with IL-8, proinflammatory cytokines that are released after this stimulation weaken intercellular contact, which probably abrogates the contact inhibition of mitosis, allowing endothelial cells to proliferate and migrate. The antiapoptotic effect is facilitated by growth factors, including transforming growth factor β (TGF-β), platelet-derived growth factor, and vascular endothelial growth factor, produced by activated leukocytes that are injected into the anterior chamber where their concentration is usually low [1]. Moreover, these growth factors facilitate the production of extracellular matrix, thus stabilizing the barrier function of the corneal endothelium. Kasparova et al. demonstrated that the suspension of activated cells used for injections contains a layer of leukocytes between a clot formed by red blood cells and plasma. The average concentration of these leukocytes is $1.341 \pm 0.12 \times 10^6$ cells/mL; of these, 35% are mononuclear cells [2]. The authors of the method also demonstrated that activated cells

continue to release cytokines and growth factors after being injected into the anterior chamber, increasing their *in vivo* concentration [3].

MATERIALS AND METHODS

This study included 12 patients with early postoperative bullous keratopathy, which developed following PE in eyes with pre-existing primary FECD. All patients were examined and treated at the Ophthalmology Clinic of the Pavlov First Saint Petersburg State Medical University. Most of the patients were females ($n = 10$). The patients' age varied between 48 and 83 years (mean age, 69.5 ± 11.6 years). The majority of participants (83.3%) were older than 61 years. All patients were diagnosed with stage 1 or 2 primary FECD (according to the classification of V.V. Volkov and M.M. Dronov, 1978) and pseudophakia. In total, 11 patients developed FECD within 1 or 2 months post cataract surgery (PE) and intraocular lens implantation; 1 patient developed FECD at 5 months post-surgery.

All patients were routinely admitted to the clinic after general examination. Ophthalmologic examination included visual acuity testing; slit-lamp indirect ophthalmoscopy (Nidek, Japan) with photo- and video-recording of pathological changes in the conjunctiva and cornea; and the biomicroscopy of the conjunctiva, cornea, and anterior segment of the eyeball. All patients also underwent confocal microscopy examination using the Confoscan-4 confocal microscope (Nidek, Japan), ocular ultrasound examination (ultrasonic A- and B-scanning, ocular biometry), ultrasonic pachymetry, optical pachymetry using the Tomey optical biometer, and tonometry using the Icare tonometer or pneumotonometry. Patients with stage 1 FECD (bullous keratopathy) showed *cornea guttata*; pathological changes were detected only in the endothelial layer of the cornea, and the estimated central corneal thickness (CCT) was 540–550 μm. Confocal microscopy revealed reduced corneal endothelial cell density (ECD), moderate polymegathism, and areas of endothelial cell loss. Patients with stage 1 FECD complained of blurred vision (primarily in the morning); none of them experienced pain.

Patients with stage 2 FECD showed persistent stromal edema detected by biomicroscopy and confocal microscopy. In three patients, ECD could not be estimated because of stromal edema. In more than 70% of the corneal area, there were Descemet's membrane (DM) folds, and CCT exceeded 590 μm. All patients showed significantly reduced visual acuity, none of them experienced pain.

Because the majority of patients presented with corneal edema, refractometry could not be performed. Mean visual acuity was 0.1 (maximum, 0.1; minimum, 0.01). None of the patients has been previously diagnosed with any disorders of the ocular fundus. However, the condition of the cornea did not allow its examination during the study.

Prior to PCT, ECD could be measured only in four patients. Mean preoperative ECD was 1269 cells/mm^2 (minimum, 912 cells/mm^2), and mean CCT was 664 μm (maximum, 804 μm; minimum, 551 μm). Intraocular pressure (IOP) was within the normal limits in all patients.

PCT was performed in an operating room. After epibulbar anesthesia, serum with activated leukocytes was slowly injected into the anterior chamber through paracentesis. Five patients received two injections at an interval of 7–10 days, and seven patients received only one injection. After PCT, all patients were followed-up for 8–12 months.

RESULTS AND DISCUSSION

In the early postoperative period (few hours after PCT), two patients experienced ocular pain and had increased IOP (up to 23 mm Hg), which was treated with IOP-lowering eye drops. The remaining patients reported no complaints except for a sprained feeling in the operated eye that lasted for several hours after PCT.

At 3 months post-PCT, mean CCT decreased to 598.4 μm (maximum, 750 μm). Complete resolution of corneal folds and restoration of corneal transparency were observed in seven patients. Mean visual acuity increased to 0.27, reaching 0.4, 0.5, and 0.7 in three patients (these patients received two injections).

Unfortunately, not all patients received the second injection, primarily because they missed their visits to the clinic. No recurrence of corneal edema was observed in any patient.

The patients' characteristic and the duration of follow-up are summarized in Table 1. Seven patients showed positive dynamics, including corneal edema resorption and a reduction in or even

Table 1

Clinical data before and after personalized cell therapy

Таблица 1

Клинические данные до процедуры персонализированной клеточной терапии и после неё

Case number	Visual acuity		Central corneal thickness (μm)		Endothelial cell density (cells/mm²)		Time of follow-up
	before PCT	after PCT	before PCT	after PCT	before PCT	after PCT	
1	0.15	0.1	622	688	n/d*	n/d*	8
2	0.1	0.4	705	716	1548	1627	8
3	0.1	0.01	727	543**	1392	1640	9
4	0.2	0.05	551**	739	912	900	12
5	0.05	0.3	765**	760	1227	2300	12
6	0.1	0.02	784	550**	n/d	1667	12
7	0.01	0.7	552**	560	n/d	1612	10
8	0.15	0.5	560	600	n/d	1500	10
9	0.25	0.2	570	760	n/d	n/d	9
10	0.05	0.3	551**	580	n/d	1200	9
11	0.1	0.3	780	540	n/d	1350	10
12	0.1	0.4	804	600	n/d	1100	10

Note: *n/d, cannot be reliably determined due to the state of the cornea; **Central corneal thickness was not determined reliably; there was considerable variation in the pachymetry results; values indicate means

a resolution of Descemet's membrane folds. CCT decreased in all patients. Confocal microscopy revealed no pathological changes in the epithelium and stroma following PCT, except for moderate polymegethism and slightly decreased pleomorphism. The positive effects were first registered at 10–14 days following PCT and remained stable during the follow-up period. Images of the eyes of patients who exhibited a good therapeutic effect following PCT are presented (Figures 1–3).

Among the patients who exhibited no therapeutic effect, five participants showed the same or decreased visual acuity following PCT. In most of these patients, CCT did not change and remained >600 μm. In some cases, CCT at pachymetry could not be reliably determined due to significant changes in the epithelium (bullae and stromal edema). All these patients had received only one injection of activated cells, and they exhibited no positive dynamics during the follow-up period.

a *b*

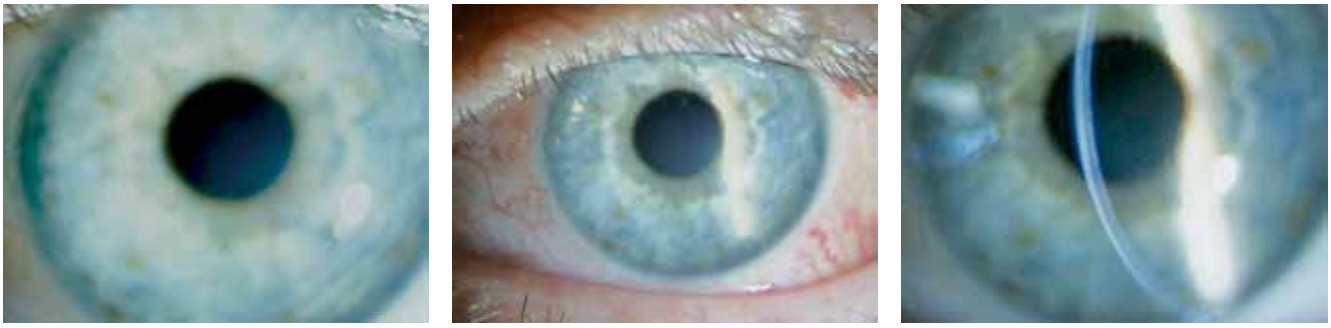
Fig. 1. Patient G.: *a* — before personalized cell therapy — pronounced stromal edema, coarse DM folds, density of endothelial cells is not reliably determined. Visual acuity is 0.1; *b* — 7 days after personalized cell therapy: reduction of stromal edema, restoration of corneal transparency, and decrease in the number of DM folds (smoothing out ≈ 70% of DM folds). Visual acuity — 0.3

Рис. 1. Пациентка Г.: *a* — до персонализированной клеточной терапии — выраженный отёк стромы, грубые складки десцеметовой оболочки (ДО), плотность эндотелиальных клеток достоверно не определяется. Острота зрения — 0,1; *b* — через 7 дней после персонализированной клеточной терапии: уменьшение отёка стромы, восстановление прозрачности роговицы и уменьшение количества складок ДО (расправление ≈ 70 % складок ДО). Острота зрения — 0,3

a *b* *c*

Fig. 2. Patient N.: *a* — before personalized cell therapy: pronounced diffuse stromal edema in the center of the cornea, single bullae, gentle DM folds, endothelial cell density is not reliably determined. Visual acuity is 0.1; *b* — 7 days after personalized cell therapy: resorption of stromal edema in the optical center, but in the paracentral zone there is an area of a local stromal edema preserved, corneal transparency is restored, there are no folds. Visual acuity — 0.4; *c* — endothelial microscopy. The density of endothelial cells after 7 days is 1729 cells/mm^2, polymegatism — 62.8%, pleomorphism — 28.5%

Рис. 2. Пациент Н.: *a* — до персонализированной клеточной терапии: выраженный диффузный отёк стромы в центре роговицы, единичные буллы, нежные складки ДО, плотность эндотелиальных клеток достоверно не определяется. Острота зрения — 0,1; *b* — через 7 дней после персонализированной клеточной терапии: резорбция отёка стромы в оптическом центре, но в парацентральной зоне сохраняется участок локального отёка стромы, восстановление прозрачности роговицы, складок ДО нет. Острота зрения — 0,4; *c* — эндотелиальная микроскопия. Плотность эндотелиальных клеток через 7 дней — 1729 кл/мм^2, полимегатизм — 62,8 %, плеоморфизм — 28,5 %



a *b* *c*

Fig. 3. Patient M.: *a* — before personalized cell therapy: moderately pronounced edema of the endothelium. The density of endothelial cells is not reliably determined, visual acuity is 0.01; *b* — 14 days after personalized cell therapy: decrease of the edema of the endothelium, restoration of corneal transparency, no DM folds. Visual acuity is 0.4, endothelial cell density is 1600 cells/mm^2; *c* — 4 months after the 2nd session of personalized cell therapy: persistent mild edema of the endothelium, visual acuity — 0.7, density of endothelial cells — 1612 cells/mm^2

Рис. 3. Пациентка М.: *a* — до персонализированной клеточной терапии: умеренно выраженный отёк эндотелия. Плотность эндотелиальных клеток достоверно не определяется, острота зрения — 0,01; *b* — через 14 дней после персонализированной клеточной терапии: уменьшение отёка эндотелия, восстановление прозрачности роговицы, складок ДО нет. Острота зрения — 0,4, плотность эндотелиальных клеток — 1600 кл/мм^2; *c* — через 4 месяца после 2-го сеанса персонализированной клеточной терапии: сохраняется лёгкий отёк эндотелия, острота зрения — 0,7, плотность эндотелиальных клеток — 1612 кл/мм^2

Confocal microscopy at 8–10 months post-PCT revealed edema in all corneal layers, thickening of Bowman's membrane, pronounced tortuosity of nerve fibers, fibrosis in the superficial layers of the corneal stroma, hyperreflexivity of the corneal stroma, and irregular orientation of collagen fibrils in the stroma. In some cases, the endothelium could not be reliably visualized; in the remaining cases, pronounced polymegethism (70%) and reduced hexagonality of endothelial cells (to 25%–30%) were observed. Ultimately, these patients underwent keratoplasty (n = 4) or descemetorhexis (n = 1).

CONCLUSION

1. PCT is a highly effective method for treating stages 1 and 2 bullous keratopathies that develop following PE in eyes with pre-existing FECD.
2. A good therapeutic effect of PCT was observed in 58.3% of the patients, and the need for ad-

ditional surgical interventions, such as keratoplasty, was eliminated.
3. PCT is currently the only effective method for treating early corneal edema following PE.
4. To achieve a good therapeutic effect, performing several injections of activated cells is recommended.
5. PCT is a well-reproducible method, and this aspect is important for its implementation into routine clinical practice once all the permissions required by the Russian Federation have been obtained.

The authors declare no conflict of interest or competing financial interest.

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