https://doi.org/10.17816/uroved46031

SUBSTITUTIONAL URETHROPLASTY WITH TISSUE-ENGINEERED STRUCTURES IN AN EXPERIMENT

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For citation: Gorelova AA, Murav'ev AN, Vinogradova TI, et al. Substitutional urethroplasty with tissue-engineered structures in an experiment. *Urology reports (St. Petersburg)*. 2020;10(3):201-208. https://doi.org/10.17816/uroved46031

Received: 03.07.2020 Revised: 21.08.2020 Accepted: 23.09.2020

Introduction. In order to exclude the difficulties arising in the course of traditional surgical interventions in the scope of substitutional urethroplasty, in recent years, alternative materials have been developed using tissue engineering. This study is devoted to the development of new tissue-engineered constructions for urethroplasty using cells of different tissue origins and biopolymers, which is an urgent problem of modern medicine.

Aim. Experimental provision of a rationale for the possibility of using tissue-engineered constructions to replace urethral defects.

Methods and materials. Two-staged, experimental, controlled study. Dedicated to the development of tissue-engineered constructions (TEC) based on biopolymers seeded with mesenchymal stem cells or buccal epithelial cells. The prepared TECs were implanted into the rabbit's urethra wall in a acute trauma model. Comparison of the results of the TECs usage with the "gold standard" – buccal urethraplasty was carried out.

Results. Urethrography showed similar results in all groups of animals, regardless the type of implanted material. No urethral patency was found, and confocal microscopy of urethral cryosections revealed the presence of nanoparticle-labeled mesenchymal stem cells / buccal epithelium cells with signs of their differentiation in the urothelial direction in the mucous layer.

Conclusion. The possibility of using tissue-engineered constructions based on biopolymers containing autologous mesenchymal stem cells or buccal epithelium cells for experimental substitutional urethroplasty was shown. The developed TECs can be used as an alternative to buccal urethroplasty in an experiment.

Keywords: urethra; tissue engineered construct; buccal epithelial cells; tissue engineering; urethroplasty.

ЗАМЕСТИТЕЛЬНАЯ УРЕТРОПЛАСТИКА ТКАНЕИНЖЕНЕРНЫМИ КОНСТРУКЦИЯМИ В ЭКСПЕРИМЕНТЕ

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Для цитирования: Горелова А.А., Муравьев А.Н., Виноградова Т.И., и др. Заместительная уретропластика тканеинженерными конструкциями в эксперименте // Урологические ведомости. – 2020. – Т. 10. – № 3. – С. 201–208. https://doi.org/10.17816/uroved46031

Поступила: 03.07.2020 Одобрена: 21.08.2020 Принята к печати: 23.09.2020

Актуальность. Для исключения сложностей, возникающих в ходе традиционных оперативных вмешательств в объеме заместительной уретропластики, в последние годы разрабатываются альтернативные материалы с использованием тканевой инженерии. Данное исследование посвящено разработке новых тканеинженерных конструкций для пластики уретры с использованием клеток различного тканевого происхождения и биополимеров, что является актуальной проблемой современной медицины.

Цель. Экспериментальное обоснование возможности применения тканеинженерных конструкций для замещения дефектов уретры.

Материалы и методы. Исследование двухэтапное, экспериментальное, контролируемое. Посвящено разработке тканеинженерных конструкций (ТИК) на основе биополимеров, заселенных мезенхимальными стволовыми клетками или клетками буккального эпителия. Приготовленные ТИК имплантировали в уретру кролика на модели ее острой травмы. Проведено сравнение результатов применения ТИК с золотым стандартом — буккальной пластикой.

Результаты. При уретрографии получены схожие результаты у всех групп животных, независимо от типа имплантированного материала. Нарушений проходимости уретры выявлено не было, а при конфокальной микроскопии криосрезов уретры обнаружено присутствие в слизистом слое меченных наночастицами мезенхимальных стволовых клеток / клеток буккального эпителия с признаками их дифференцировки в уротелиальном направлении.

Заключение. Показана возможность использования для заместительной уретропластики в экспериментальных условиях тканеинженерных конструкций на основе биополимеров, содержащих аутологичные мезенхимальные стволовые клетки или клетки буккального эпителия. Разработанные ТИК можно использовать в качестве альтернативы буккальной уретропластике в эксперименте.

Ключевые слова: уретра; тканеинженерные конструкции; клетки буккального эпителия; тканевая инженерия; уретропластика.

INTRODUCTION

Surgery is the main treatment for the pathologies of urethra diseases, and in some cases, it requires unconventional approaches in planning and technique [1, 2]. There are several options for replacement and augmentation urethroplasty, the choice of which depends on the pathological process location, etiology, and extent of the lesion. The individual's own tissues (e.g., preputium skin grafts, skin of the penis, scrotum, perineum, grafts of the *tunica vaginalis* of the testicle, grafts from the buccal mucosa, or bladder mucosa) are used as implantable materials [3].

In addition to traditional flaps and grafts for replacement urethroplasty, alternative materials are currently being developed using tissue engineering, which are aimed at eliminating difficulties observed in traditional surgical interventions, associated with insufficient graft length as well as complications in the donor area and an increase in the intervention duration [4].

Our own experience of using tissue-engineered constructs containing mesenchymal stem cells (MSCs) to replace bladder defects demonstrated MSC's ability to form structures similar to urothelium [5, 6], which enables to expand the scope of their application.

Our research is focused on the development of new tissue-engineered constructs for urethroplasty, using cells of various tissue origin and biopolymers, which is an urgent problem of modern medicine.

This study aimed to substantiate experimentally the possibility of using tissue-engineered constructs to replace urethral defects.

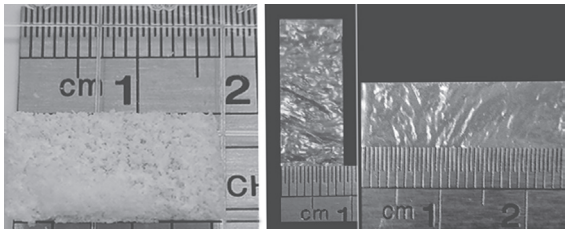
MATERIALS AND METHODS

The study was two-stage, experimental, and controlled. At stage 1 *in vivo*, the study included 10 sexually mature nonlinear white male rats weighing 393.7 ± 29.97 g (350–444 g) within the analysis of scaffold biodegradation.

At stage 2, the created tissue-engineered constructs (TECs) were implanted in the models of acute urethral trauma in experimental animals (rabbits). This stage of the study included 31 sexually mature male chinchilla rabbits weighing 3919.1 ± 378.01 g (3,366–5,145 g).

The animals were kept under standard conditions in accordance with the current regulatory documents and were used in the study after a 2-week quarantine; no external signs of pathology nor abnormalities in general behavioral reactions were noted.

Two types of scaffolds were prepared. For MSC inoculation, we used a porous matrix consisting of poly-(D, L)-lactide (PL) and polycaprolactone (PC) (Fig. 1, *a*).



a *b*

Fig. 1. Samples of prepared scaffolds: *a* — porous two-layer scaffold based on PL + PC; *b* — flat two-layer scaffold based on PLG + PLC
Рис. 1. Образцы приготовленных скаффолдов: *a* — пористый двуслойный из ПЛ + ПК; *b* — плоский двуслойный из ПЛГ + ПЛК

The porous layer of the two-layer matrix, consisting of poly (D, L)-lactide, created favorable conditions for the subsequent cultivation of MSCs.

For urethroplasty using buccal epithelial cells (BECs), a two-layer scaffold based on polyhydroxyethers was developed (Fig. 1, *b*). The inner layer that comes into contact with urine was formed from poly-L-lactide-caprolactone (PLC) (70/30) (h = 3.8 dl/g, Purac). The solid- and liquid-tight structure provides a barrier function (from urine) and mechanical strength to the entire structure. The second layer, on which the buccal epithelial cells were inoculated, was prepared with poly-L-lactide-glycolide (PLG) (85/15) (h = 3.13 dl/g, Purac), which is most favorable for the cultivation of BEC. The scaffolds were sterilized by ozonation.

The biodegradation of scaffolds was studied in 10 nonlinear white male rats. The scaffolds PL + PC and PLC-PLG were implanted subcutaneously in rats.

Surgical protocol

Ten 1.0-cm-long transverse incisions (five on each side) were made with the subject under general anesthesia using preparations of tiletamine hydrochloride/zolazepam hydrochloride (Zoletil, Virbac SA, France) at 25 mg/kg body weight administered intramuscularly and xylazine hydrochloride (Bioveta, Czech Republic) as 2% solution at 1.0–1.5 ml administered intramuscularly at the back, on both sides of the vertebral line (Fig. 2). The first pair of incisions was for control, the

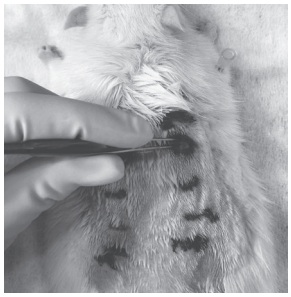


Fig. 2. Subcutaneous implantation of scaffolds in the rat back
Рис. 2. Подкожная имплантация скаффолдов в область спины крысы

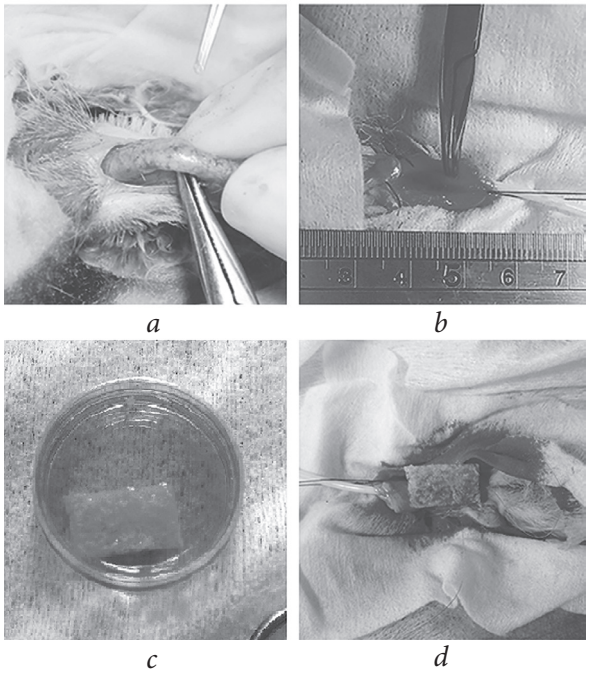


Fig. 3. Urethroplasty with implantation of the TEC, based on PL + PC with MSCs: *a* – the urethra is exposed dorso-laterally; *b* – the lumen of the urethra is opened; *c* – TEC with MSC; *d* – comparison of the TEC and the edges of the urethral defect

Рис. 3. Уретропластика с имплантацией тканеинженерной конструкции, состоящей из ПЛ + ПК с мезенхимальными стволовыми клетками: *a* — уретра выделена дорсо-латерально; *b* — вскрыт просвет уретры; *c* — тканеинженерная конструкция с мезенхимальными стволовыми клетками; *d* — сопоставление тканеинженерной конструкции и краев дефекта уретры

second and third pairs were for subcutaneous implantation of PL + PC scaffolds, and the fourth and fifth ones were used for PLC-PLG scaffolds. The wounds were then sutured, postoperative wounds were treated with an antiseptic solution, and an aseptic dressing was applied.

The rats were withdrawn from the experiment after 1 and 4 weeks (five rats at each time) with the use of tiletamine hydrochloride/zolazepam hydrochloride (Zoletil, Virbac SA, France) and the muscle relaxant xylazine hydrochloride (Rometar, Bioveta, Czech Republic) in doses five times higher than the therapeutic ones. A macroscopic evaluation of the results was performed.

Stage 2 of the study included creation and implantation of TECs on a model of acute urethral injury in experimental animals. The rabbits were distributed into three groups depending on the graft used: Group 1 included 9 rabbits with a scaffold based on PL + PC with MSCs implanted into the urethra dorsolaterally. Group 2 consisted of 15 rabbits with a scaffold based on PLG + PLC with BEC implanted. Group 3 included 4 rabbits which underwent buccal urethral grafting.

For the subsequent identification of cells in the experiment *in vivo*, MSCs and BECs were labeled with superparamagnetic nanoparticles of iron oxide (Fe_3O_4, SPION).

The course of the surgical intervention is presented in Fig. 3.

With the subject under general anesthesia (Zoletil, Virbac SA, France, at 25 mg/kg body weight intramuscularly, and Rometar, Bioveta, Czech Republic, in the form of a 2% solution at 1.0–1.5 ml intramuscularly), a no. 6 Foley catheter was inserted into the bladder along the urethra. The urethra with a spongy body was isolated using a longitudinal incision of the skin of the penis 3 cm along the ventral surface; by blunt and sharp dissection on the left, a mucosal defect of 7 × 2 mm was made on the dorsal surface. The rabbits of group 3 underwent hydro-preparation of the buccal mucosa; a 1.5 × 0.5 cm mucous graft was taken, which was cleaned of underlying tissue and fixed to the albugineous tunic of the cavernous body and the edges of the urethral defect with interrupted sutures (Vicryl 6/0). In animals of groups 1 and 2, the scaffolds were attached to the edges of the defect and the albugineous tunic of the cavernous body with separate interrupted sutures (Vicryl 6/0). The wound was sutured in layers. The urethral catheter was fixed to the glans penis with an interrupted suture and cut off at the meatus level. Antibiotic prophylaxis was performed with cefazoline at 10 mg/kg administered intramuscularly 1 hour before the surgery; additionally, in the postoperative period, cefazoline 10 mg/kg was administered 3 times a day for 5 days intramuscularly.

RESULTS

The objectives of our study included the study of mechanical characteristics of scaffolds, which are described in Table 1.

Table 1 / Таблица 1

Mechanical properties of scaffolds
Механические свойства скаффолдов

Scaffold	Width, mm	Thickness, mm	Strength, MPa	Elongation at rupture, %	Elastic coefficient, MPa
PL + PC	3	1.2	0.19 ± 0.09	15.9 ± 3.4	1.68 ± 0.09
PLG + PLC	3	0.2	0.22 ± 0.07	19.1 ± 4.1	2.16 ± 0.18

Note. $p > 0{,}05$.

The table reveals that a scaffold based on PLG + PLC is more elastic and durable. During surgical interventions, no suture eruptions were noted in any case. The mechanical-strength characteristics of the scaffolds determined as results of this study are comparable with the corresponding characteristics of the native rabbit urethra, described by Feng et al. [7].

To assess the toxicity of the materials used in scaffolds, namely, poly-L-lactide-caprolactone (PLC, 70/30) and poly-L-lactide-glycolide (PLG, 85/15), the viability of mesenchymal stem cells was determined in vitro under conditions of their cultivation on synthesized polymer films (Fig. 4).

Photos taken on day 1 after cultivation of MSCs (Fig. 4) show that the cells retain their integrity, spread equally well, and adhere both to the test and control materials (glass). These criteria indicate the viability of cells and the absence of toxicity of the materials.

When studying the biodegradation of scaffolds implanted subcutaneously in rats, partial biodegradation of the implants was identified after 1 week, and full biodegradation was detected after 4 weeks (Fig. 5). In this case, the greatest degradation of scaffold based on PLG + PLC was macroscopically revealed after 1 week.

Thus, the study of new scaffolds based on poly-L-lactide-caprolactone and poly-L-lactide-glycolide showed that these matrices have good mechanical characteristics. However, when comparing them, PLG + PLC scaffolds revealed greater strength and elasticity. Biodegradation studies have shown that all scaffolds are completely absorbed by week 4. When comparing them, the biodegradation process occurs faster in PLG + PLC scaffolds.

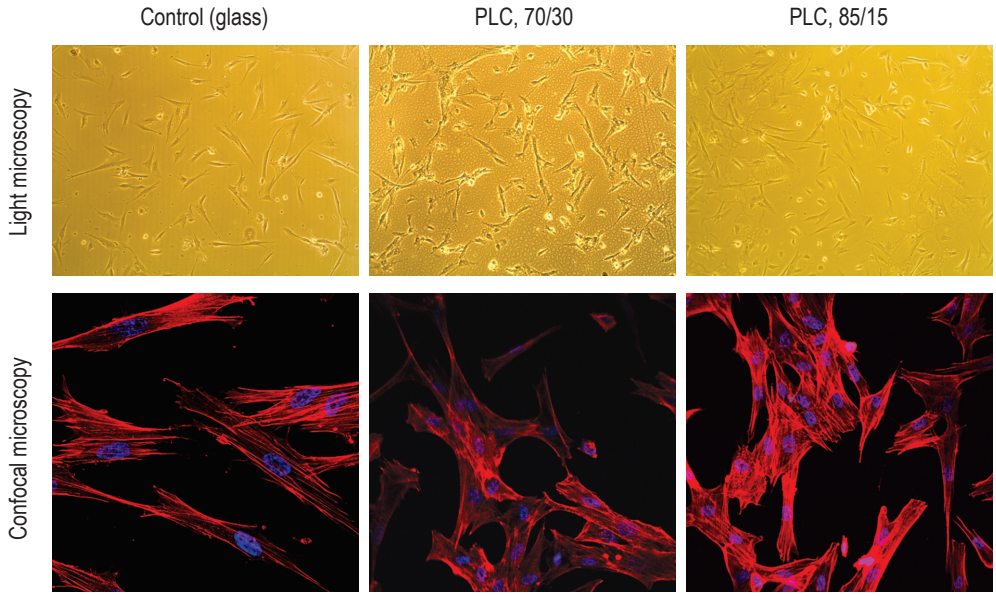
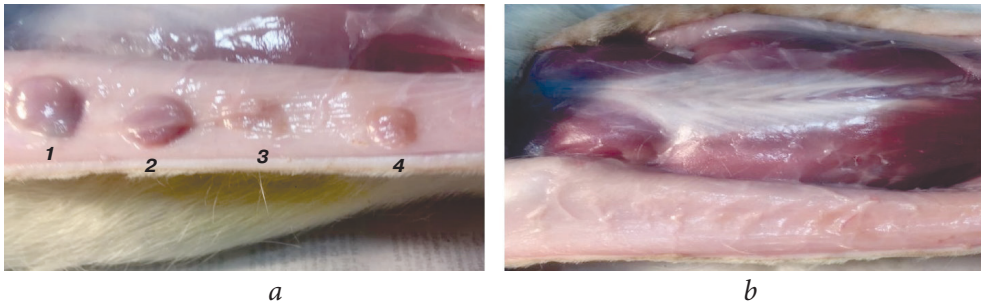
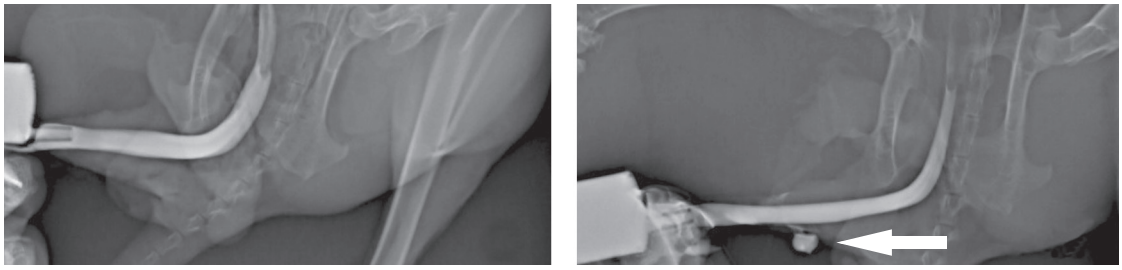


Fig. 4. Human bone marrow mesenchymal stem cells after 1 day of cultivation on polymer films (light microscopy ×4; confocal microscopy ×40)
Рис. 4. Мезенхимные стромальные клетки костного мозга человека через 1 сутки культивирования на полимерных пленках (световая микроскопия, ×4; конфокальная микроскопия, ×40)



a *b*

Fig. 5. The process of scaffold biodegradation — the studied scaffolds (*1*, *2* – PL + PC; *3*, *4* – PLC + PLG) were implanted subcutaneously in rats: *a* – 1 week after implantation, the intervention zone is determined; *b* – after 4 weeks, the intervention zone is not visualized macroscopically
Рис. 5. Процесс биодеградации скаффолдов — подкожно крысам имплантированы исследуемые скаффолды (*1*, *2* — ПЛ + ПК; *3*, *4* — ПЛК + ПЛГ): *a* — через 1 нед. после имплантации определяется зона вмешательства; *b* — через 4 нед. макроскопически зона вмешательства не визуализируется



a *b*

Fig. 6. Retrograde urethrograms: *a* — the lumen of the urethra is preserved; *b* — the extravasation of the contrast agent outside the lumen of the urethra
Рис. 6. Ретроградные уретрограммы: *a* — просвет уретры сохранен; *b* — экстравазация контрастного вещества за пределы просвета уретры

To assess the state of the urethra in the postoperative period, retrograde urethrography was performed in all rabbits after autopsy (Fig. 6). In animals of all three groups, the patency of the urethra was retained.

Fig. 6 demonstrates complete patency of the urethra; no narrowing and diverticula were identified. In two rabbits previously diagnosed with urethrocutaneous fistula (group 2), extravasation of the contrast agent beyond the urethral lumen was noted (Fig. 6, *b*).

Thus, regardless of the type of material implanted for replacement urethroplasty, the urethral lumen, a crucial indicator, was preserved.

After the preparation of the urethra macro-preparations, the implantation zone was assessed; the results are presented in Table 2.

Data presented in Table 2 demonstrate that by the third month of follow-up, in some animals with tissue-engineered constructs implanted, the urethral tissue restored completely. Thus, the implantation zone could be visualized only in 66.7% and 88.9% of experimental animals of groups 1 and 2, respectively.

Macroscopic assessment of the implantation zone showed no implant failure, narrowing, or diverticula of the urethra in any group (Fig. 7).

In groups 1 and 2, 1 and 2 months after surgery, the implantation zone was visualized in all rabbits (Fig. 7, *a*). However, after 3 months, in groups 1 and 2, the implantation zone was visualized in 66.7% and 88.9%, respectively (Fig. 7, *b*). The buccal graft was clearly seen in all animals (Fig. 7, *c*). Two previously described urethrocutaneous fistulas were found in the group of rabbits with implanted TECs based on PLG + PLC with buccal epithelial cells (Fig. 7, *d*). Statistical analysis did not reveal a significant correlation between the implanted materials and possibility of fistulous tract formation (the significance level p of Fisher's exact test in intergroup comparison was >0.05).

To identify the presence of cells labeled with nanoparticles in the biopsy specimen, cryosections were prepared. SPION-labeled MSCs in the wall of the urethra were assessed at different times after surgery (group 1 rabbits). An intact urethra was used as a control (Fig. 8). Nuclei were stained with DAPI (blue) and detected using a diode laser (405 nm). SPIONs were visualized as red light on reflected laser scanning (504 nm). The preparations were additionally stained with specific antibodies (cytokeratin AE1/AE3), secondary antibodies labeled with FITC (green) (Fig. 8, urothelium), and anti-αSMA antibodies (Fig. 8, muscle layer).

Fig. 7 presents the co-localization of nanoparticle-labeled MSCs with AE1/AE3 cytokeratin-stained urothelium, which proves the possibility of MSC differ-

Table 2 / Таблица 2

Macroscopic characteristics of the implantation zone
Макроскопическая характеристика зоны имплантации

Group (*n*)	Terms of autopsy, months	Visualization of the implantation area, *n* (%)	Implant failure, *n* (%)	Implant visualization, *n* (%)	Diverticulum, *n* (%)	Narrowing, *n* (%)	Fistula, *n* (%)
No. 1 (9)	1	3 (100)	0	0	0	0	0
	2	3 (100)	0	0	0	0	0
	3	2 (66.7)	0	0	0	0	0
No. 2 (15)	1	3 (100)	0	0	0	0	0
	2	3 (100)	0	0	0	0	0
	3	8 (88.9)	0	0	0	0	2 (22.2)
No. 3 (4)	3	4 (100)	0	4 (100)	0	0	0

entiation into neourothelial cells. In the muscle layer, nanoparticle-labeled MSCs were detected; however, their co-localization with smooth muscle cells stained with anti-αSMA antibodies was not noted. This arrangement of the labeled cells indicates that MSCs within the TEC implanted into the urethra are involved in the formation of the muscle layer, but do not undergo differentiation in the smooth muscles.

The presence of BEC labeled with nanoparticles in biopsy samples in animals of group 2 was evaluated using the same methods as in animals of the group 1 (Fig. 9).

Co-localization of BECs stained with AE1/AE3 cytokeratin and those containing nanoparticles in group 2 at week 12 also indicated possible differentiation into neourothelial cells. No co-localization was found in the muscle layer, and no cells labeled with nanoparticles were found in biopsy samples of group 3 and in intact tissues.

Thus, data obtained by confocal microscopy reveal conclusively not only the preservation of the viability of cells used in the composition of the TECs for 3 months but also their acquisition of properties characteristic of urothelium.

CONCLUSION

As a result of the study, the possibility of using tissue-engineered constructs based on biopolymers containing autologous mesenchymal stem cells or buccal epithelium cells for replacement urethroplasty under experimental conditions has been conclusively demonstrated. These tissue-engineered constructs can be used as an alternative to buccal urethroplasty in experiments.

Obtaining superparamagnetic iron oxide nanoparticles was supported by the Russian Foundation for Basic Research (project no. 19-58-55001 China_a). *In vitro* experiments (cell cultivation, development, and preparation of tissue-engineered constructs) were conducted under state assignment no. 0103-2019-0012.

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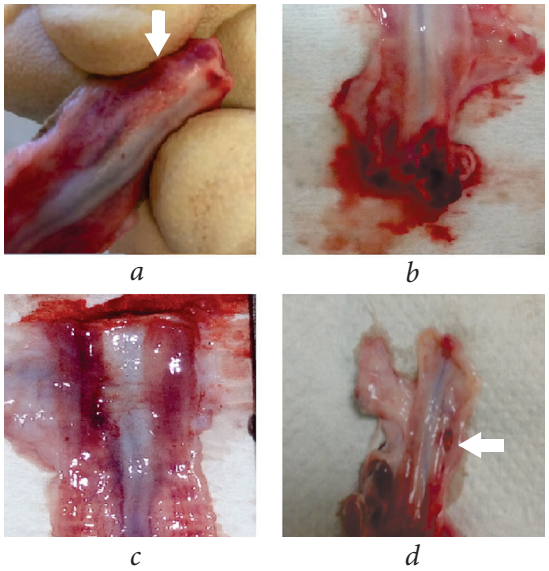

Fig. 7. Macro preparations of the rabbit urethra: *a* – visualization of the TEC implantation zone (group 1); *b* – the TEC implantation zone is not visualized (group 2); *c* – visualization of the buccal graft; *d* – urethrocutaneous fistula (arrow)

Рис. 7. Макропрепараты уретры кролика: *a* — визуализация зоны имплантации тканеинженерной конструкции (группа 1); *b* — зона имплантации не визуализирована (группа 2); *c* — визуализация буккального графта; *d* — уретро-кожный свищ (стрелка)

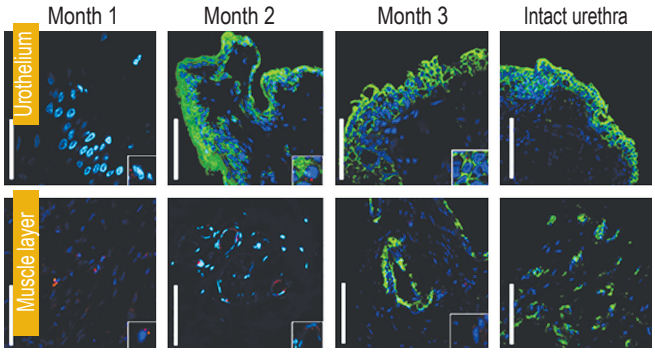

Fig. 8. Confocal microscopy, visualization of nanoparticles in the mucous layer at different time after implantation of TECs with MSCs. The scale bars correspond to 100 μm

Рис. 8. Конфокальная микроскопия, визуализация наночастиц в слизистом слое на разных сроках после имплантации тканеинженерной конструкции с мезенхимальными стволовыми клетками. Масштабные отрезки соответствуют 100 мкм

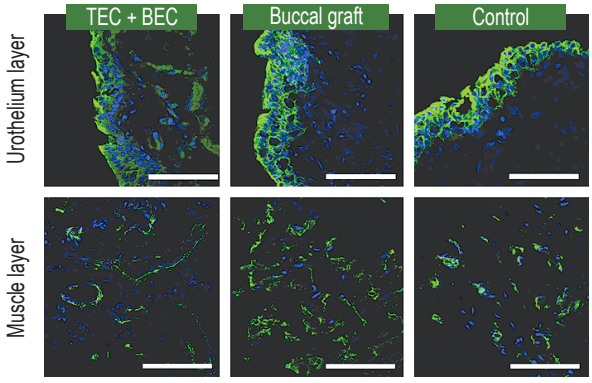

Fig. 9. Confocal microscopy, visualization of nanoparticles in the mucous layer 12 weeks after implantation of TECs with buccal epithelial cells . The scale bars correspond to 100 μm

Рис. 9. Конфокальная микроскопия, визуализация наночастиц в слизистом слое через 12 недель после имплантации тканеинженерной конструкции (ТИК) с клетоками буккального эпителия (КБЭ). Масштабные отрезки соответствуют 100 мкм

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