AN EXPERIMENT ON BIOLOGICAL OBJECTS: COMPOSITE FACIAL GRAFT CROSS-TRANSPLANTATION

Daikhes NA[1], Nazaryan DN[1], Gileva KS[2], Mokhirev MA[1], Lyashev IN[1], Zakharov GK[1], Fedosov AV[1], Potapov MB[1], Batyrev AV[1] ✉, Karneeva OV[1]

[1] Federal Scientific and Clinical Center of Otorhinolaryngology under the Federal Medical-Biological Agency (FMBA) of the Russian Federation, Moscow, Russia

[2] Petrovsky Russian Scientific Center for Surgery, Moscow, Russia

Facial graft transplantation remains the operation of choice for patients with extensive tissue defects in the maxillofacial region. This study aimed to set up an experiment on biological objects, develop and test a combined facial graft cross-transplantation technique, select the anesthetic aid allowing to reduce the risks of perioperative complications, improve survivability of the subjects by reducing the duration of surgical intervention, develop a postoperative therapy and rehabilitation protocol, assess detection of an acute rejection reaction and develop the immunosuppressive therapy protocol. We conducted three series of facial graft transplantation surgeries on 26 minipigs and tested the typical component combinations and flap designs. At all stages of the experiment, we managed to have the subjects surviving for over 30 days without disrupting their vital functions. The immunosuppression procedure was developed and tested. The chosen technique allows transplanting two grafts within a single surgery on one pair.

Keywords: face transplant, microsurgery, facial flap, composite flap

Funding: FMBA applied research, subject "Research of metabolic, morphometric and functional characteristics of tissues and organs after head and neck area surgery involving physical and laser-conversion digital technologies" ("ChLH-18").

Author contribution: Daikhes NA, Nazaryan DN — work organization, article editing; Gileva KS, Mokhirev MA, Lyashev IN, Zakharov GK, Fedosov AV, Potapov MB — participation in the experimental part of the work; Batyrev AV — participation in the organization and experimental part of the work, article authoring; Karneeva OV — participation in the organization of work.

Compliance with ethical standards: the living conditions of animals, care and all manipulations they were subjected to meet the experimental model research standards.

✉ **Correspondence should be addressed:** Alexey V. Batyrev
Volokolamskoe shosse, 30/2, k. 443, Moscow, 123182; craniofacial@yandex.ru

Received: 01.10.2020 **Accepted:** 14.11.2020 **Published online:** 29.11.2020

DOI: 10.47183/mes.2020.018

ПЕРЕКРЕСТНАЯ ПЕРЕСАДКА КОМБИНИРОВАННОГО ЛИЦЕВОГО ТРАНСПЛАНТАТА В ЭКСПЕРИМЕНТЕ НА БИООБЪЕКТАХ

Н. А. Дайхес[1], Д. Н. Назарян[1], К. С. Гилева[2], М. А. Мохирев[1], И. Н. Ляшев[1], Г. К. Захаров[1], А. В. Федосов[1], М. Б. Потапов[1], А. В. Батырев[1] ✉, О. В. Карнеева[1]

[1] Национальный медицинский исследовательский центр оториноларингологии Федерального медико-биологического агентства России, Москва, Россия

[2] Российский научный центр хирургии имени Б. В. Петровского, Москва, Россия

Пересадка лицевого трансплантата остается операцией выбора для пациентов с обширными дефектами тканей челюстно-лицевой области. Целью работы было в эксперименте на биообъектах разработать и апробировать методику перекрестной пересадки комбинированного лицевого трансплантата, подобрать анестезиологическое пособие с целью снижения рисков периоперационных осложнений, улучшения показателей выживаемости особей за счет сокращения длительности хирургического вмешательства и разработать протокол послеоперационной терапии и реабилитации особей, оценки диагностики острой реакции отторжения и отработки иммуносупрессивной терапии. В трех сериях операций по пересадке лицевых трансплантатов на 26 минипигах были апробированы типичные комбинации компонентов и дизайны лоскута. На всех этапах эксперимента команда добилась выживания особей более 30 дней, без нарушения жизненных функций. Отработана схема иммуносупрессии. Выбранная методика позволяет проводить две пересадки за одно хирургическое вмешательство внутри одной пары.

Ключевые слова: трансплантация лица, микрохирургия, лицевой лоскут, композитный трансплантат

Финансирование: согласно гранту ФМБА на выполнение прикладной научно-исследовательской работы по теме «Исследование метаболических, морфометрических и функциональных характеристик тканей и органов после операций в области головы и шеи на основе применения физических и лазерно-конверсионных цифровых технологий» («ЧЛХ-18»).

Вклад авторов: Н. А. Дайхес, Д. Н. Назарян — организация работы, редактирование статьи; К. С. Гилева, М. А. Мохирев, И. Н. Ляшев, Г. К. Захаров, А. В. Федосов, М. Б. Потапов — участие в экспериментальной части работы; А. В. Батырев — участие в организации и экспериментальной части работы, написание статьи; О. В. Карнеева — участие в организации работы.

Соблюдение этических стандартов: условия содержания животных, уход и все проводимые с ними манипуляции соответствовали стандартам работы с экспериментальными моделями.

✉ **Для корреспонденции:** Алексей Владимирович Батырев
Волоколамское шоссе, д. 30/2, к. 443, г. Москва, 123182; craniofacial@yandex.ru

Статья получена: 01.10.2020 **Статья принята к печати:** 14.11.2020 **Опубликована онлайн:** 29.11.2020

DOI: 10.47183/mes.2020.018

Currently, the main method for reconstruction of extensive head and neck defects is free autograft transplantation [1–3]. However, the loss of such structures as lips, eyelids, nose makes allotransplantation of a composite facial flap the only approach allowing fully-fledged rehabilitation [4–6].

To date, 40 composite facial graft transplantation surgeries have been executed in the world. The first successful operations were performed in 2005 [7], yet this type of surgical intervention remains unique and requires involvement of highly qualified specialists in the preparation, intervention itself, further observation and rehabilitation [8]. The high immunogenicity of the skin, which increases the risks of graft rejection, is still a big problem faced by the teams performing such manipulations. Currently, there is no single approach to the intervention, with a

Fig. 1. Experimental animals in the immediate postoperative period

Fig. 2. Minipigs on the 14th day after the cross-transplantation

number of solutions suggested. Humanity of experiments and preservation of life of experimental animals remain an important requirement.

To date, laboratory mice remained the animals of choice for experimental facial graft transplantations [9].

This study aimed: 1) to develop and test experimentally the composite facial graft cross-transplantation technique on minipigs; 2) to develop and test on the subjects postoperative therapy and rehabilitation courses, assess the acute rejection diagnostics approach, develop a competent immunosuppressive therapy plan; 3) to test the anesthetic aid used to reduce the risks of perioperative complications.

METHODS

The participants of the experiment carried out three series of facial graft transplantation surgeries on specially selected animals, minipigs, as biological models.

For the experiment, 26 closely related animals were selected: brothers aged from 8 to 24 months, weighing 10–20 kg [10, 11].

The surgeries involved two animals in parallel and took place in a prepared operating room. The participants used standard surgical instruments. An operating microscope was used microscopy stage. As part of the preparation for surgery, we marked the composite facial graft on one animal and, to ensure the maximum possible level of precision, used a template to repeat the same on the other animal. Collecting the grafts, we mobilized the soft tissue components of the flaps while preserving vital structures, keeping the vascular bundles intact to the level of their branching from the external carotid arteries and connecting to the jugular veins, and isolating the facial nerve for subsequent neuroraphy. The bone parts of the grafts were mobilized atraumatically with a piezosurgical tool; after transplantation, they were fastened with Conmet miniplates and miniscrews. Post-surgery, we took biopsy samples dynamically on the 7th, 14th, and 21st days. The samples were used to verify the reparative processes. In case of any signs of rejection, the biopsy samples were collected outside the adopted schedule. We took photos and recorded videos at all stages of the experiment (Fig. 1, 2).

We considered various combinations of flaps with the aim to include the most common flaps designs in our work (Table 1).

Execution of the 1st stage

At the first stage, we carried out experimental facial graft cross-transplantations on five pairs of minipigs (brothers, age — 24 months, weight — 16–20 kg). In the context of these surgeries, we tested and applied the main techniques and flap designs, with the technique application involving all the key stages (Fig. 11–13):

– facial musculocutaneous flap from the buccal, parotid regions;

– composite skin-musculoskeletal flap from the buccal, parotid regions and the lower jaw;

– composite skin-musculoskeletal flap form the paraorbital, buccal, parotid regions and the upper jaw.

Table 1. Flap designs used at different stages of the experiment

Number of animals	Age (months)	Graft design
1st stage		
4	24	Facial musculocutaneous flap from the buccal, parotid regions (Fig. 3, 4)
4	24	Composite skin-musculoskeletal flap from the buccal, parotid regions and the lower jaw (Fig. 5, 6)
2	24	Composite skin-musculoskeletal flap form the paraorbital, buccal, parotid regions and the upper jaw
2nd stage		
2	24	Facial musculocutaneous flap from the buccal, parotid, lower paraorbital regions (Fig. 7, 8)
2	8	Facial musculocutaneous flap from the buccal, parotid, lower paraorbital regions (Fig. 9, 10)
2	24	Facial musculocutaneous flap from the parotid region with auricle and buccal part
2	8	Facial musculocutaneous flap from the parotid region with auricle and buccal part
3rd stage		
4	8	Facial musculocutaneous flap from the buccal and parotid regions, with neuroanastomoses made in the region of facial nerve branches
4	8	Facial musculocutaneous flap from the parotid region with external part of the auricle, buccal region, with neuroanastomoses made in the region of facial nerve branches

Fig. 3. Facial musculocutaneous flap from the buccal, parotid regions (first subject)

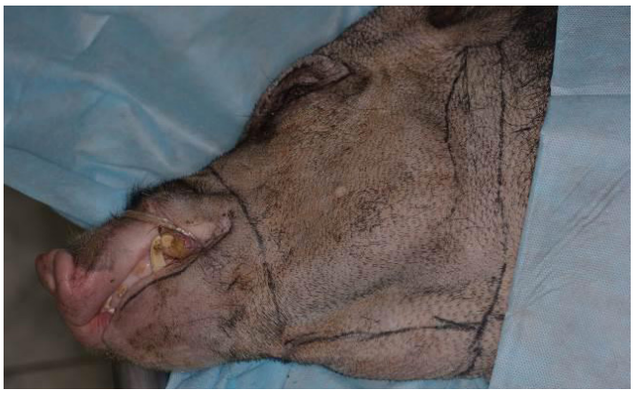

Fig. 4. Facial musculocutaneous flap from the buccal, parotid regions (second subject)

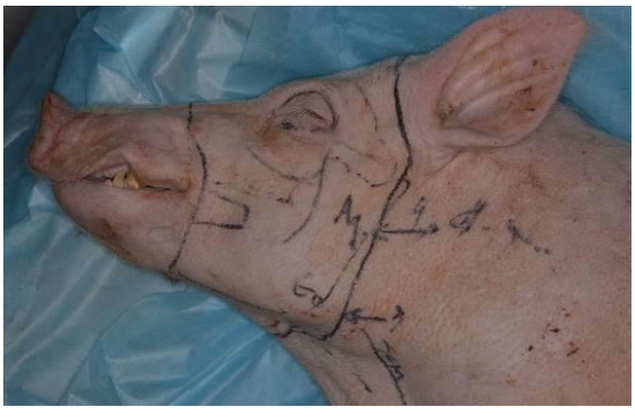

Fig. 5. Composite skin-musculoskeletal flap from the buccal, parotid regions and the lower jaw (first subject)

Fig. 6. Composite skin-musculoskeletal flap from the buccal, parotid regions and the lower jaw (second subject)

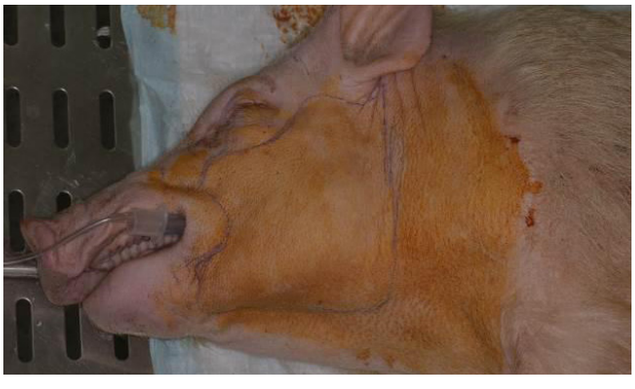

Fig. 7. Facial musculocutaneous flap from the buccal, parotid, lower paraorbital regions (first subject)

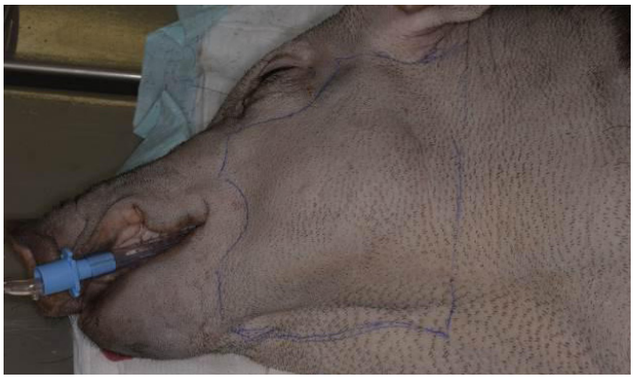

Fig. 8. Facial musculocutaneous flap from the buccal, parotid, lower paraorbital regions (second subject)

Fig. 9. Facial musculocutaneous flap from the parotid region with auricle and buccal part (first subject)

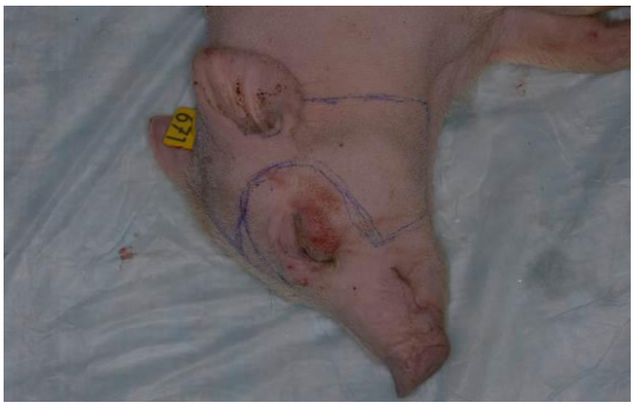

Fig. 10. Facial musculocutaneous flap from the parotid region with auricle and buccal part (second subject)

Surgical interventions were performed under intravenous anesthesia (rometar 0.15 mg/kg + zoletil-100 2 mg/kg) without anesthetic support. The average time of surgery was 14 hours.

Post-surgery, the animals received an antibacterial drug (Baytril for 14 days) and 120 mg of prednisolone i.m. OD throughout the entire follow-up period.

On the 5th day after the operation, two animals developed edema. They were subjected to pulse therapy, and their scheduled prednisolone intake was increased to 240 mg. Five days after, we registered thrombosis of the anastomoses caused by the intensified vascular reaction to hyperergic response of the recipient's body.

Execution of the 2nd stage

At the second stage, we cross-transplanted facial grafts on four pairs of animals (two pairs — brothers, age — 24 months, weight — 20 kg; two pairs — brothers, age — 8 months, weight — 8 kg).

In this experiment, we tested cross-transplantation of the following flap designs:

– facial musculocutaneous flap from the buccal, parotid, lower paraorbital regions;

– facial musculocutaneous flap from the parotid region with auricle and buccal part.

Surgical interventions were performed with anesthetic aid, under intravenous sedation (rometar 0.15 mg/kg, zoletil-100 2 mg/kg, propofol 4 mg/kg, xyla 0.2 ml/kg) and supervision of anesthesiologists. The average time of surgery was 10 hours.

Post-surgery, the animals received 3 ml of Baytril i.m. OD (antibacterial therapy) and 16 mg of dexamethasone i.m. OD (immunotherapy) throughout the entire follow-up period.

Same as at the 1st stage of the experiment, we registered a delayed development of rejection. Clinical manifestations were relieved by pulse therapy (360 mg of solumedrol i.m.).

On the 21st day post-surgery, we collected histological material from the place of fusion of the transplanted flap and the recipient's tissues for histological control.

Execution of the 3rd stage

At the 3rd stage, we cross-transplanted facial grafts on four pairs of animals (four pairs — brothers, age — 8 months, weight — 10 kg). Analysis of the results of the previous stages allowed us to adjust perioperative therapy and the anesthesia protocol. Intra- and post-surgery, we subjected the animals to immunosuppressive therapy [12].

To prevent immediate loss of grafts for immunological reasons, we determined blood group compatibility and performed the microlimphocytotoxic test on the eve of the operation. The fact that each animal was both a donor and a recipient simultaneously was factored in. Individual blood compatibility was checked with the help of room temperature crossmatching.

Based on the results of a series of immunological tests, we made four pairs of animals that underwent a total of eight transplantation surgeries. In each case, the individual compatibility and the microlymphiphocytotoxic tests returned negative.

In this experiment, we continued testing composite flap designs, namely:

– facial musculocutaneous flap from the buccal and parotid regions, with neuroanastomoses made in the region of facial nerve branches;

– facial musculocutaneous flap from the parotid region with external part of the auricle, buccal region, with neuroanastomoses made in the region of facial nerve branches (Fig. 14).

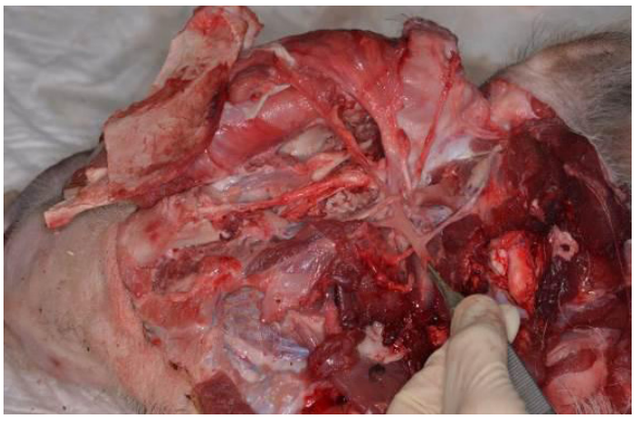

Fig. 11. Intraoperative picture taken after dissection of the composite skin-musculoskeletal flap from the buccal region

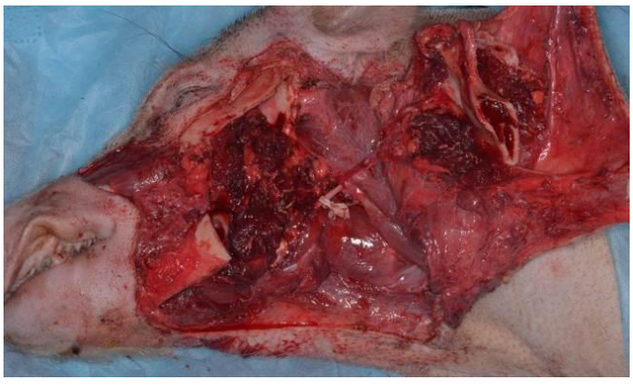

Fig. 12. Intraoperative picture taken after dissection of the composite skin-musculoskeletal flap from the buccal region and the lower jaw

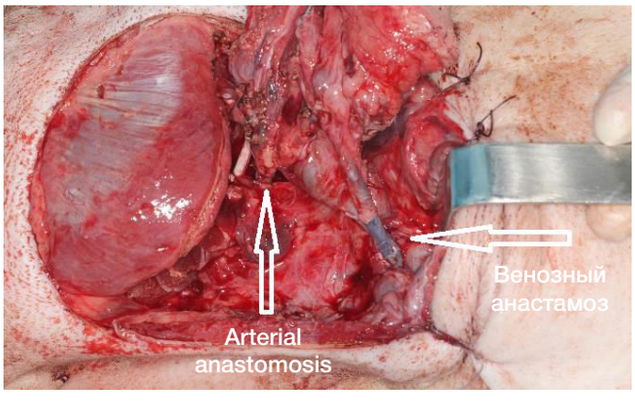

Fig. 13. Intraoperative picture taken after vascular anastomoses were made

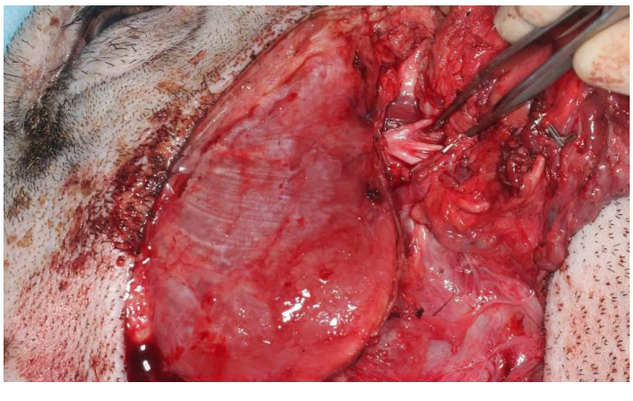

Fig. 14. Intraoperative picture taken after exposition of the facial nerve's trunk and branches

Table 2. Follow-up time at each stage of the experiment

Number of animals	Age (months)	Flap observation time
1st stage		
Two pairs (recipient — donor)	24	36 days
2nd stage		
Two subjects from different pairs	8	30 days (histological confirmation on the 21st day of the primary adhesion process)
3rd stage		
Two subjects from different pairs (administration of tacrolimus)	8	30 days (histological confirmation on the 14th day of the primary adhesion process)

Table 3. Survival of the animals after surgery

Number of animals	Duration
1st stage	
8 out of 10 (80%)	Over 30 days
2nd stage	
7 out of 8 (87.5%)	Over 30 days
3rd stage	
7 out of 8 (87.5%)	Over 30 days

Surgical intervention was performed with anesthetic aid under intravenous sedation (zoletil-100 2 mg/kg, propofol — 4 mg/kg, xyla — 0.2 ml/kg). The average time of surgery was 8 hours.

Based on the additional advice received through consultations with transplantologists and anesthesiologists, we adjusted the drug therapy as follows.

Pre-surgery:

8 hours before intervention — low molecular weight heparins (clexane), s.c.;

antibiotic therapy — 1 ml of interspectin i.v. 30 minutes before the incision.

Intraoperatively, two pairs of subjects received:

0.15 mg/kg of Prograf i.v.;

heparin before the blood flow was resumed.

Post-surgery, experimental models received: antibiotics (1 ml of interspectin per 10 kg of weight i.m. OD) for 14 days with the aim to prevent secondary bacterial complications;

immunosuppressive drug (Solumedrol 160 mg/m) throughout the follow-up period.

We did not register pronounced manifestations of flap rejection post-surgery. The persisting edema were attributed to the volume of intervention and hypersecretion of the salivary gland.

RESULTS

We had the subjects surviving long-term at all stages of the experiment, which indicates humane use of animals. Post-surgery, their vital functions remained unchanged (Table 2). We succeeded in improving the survival rate of models after surgical interventions (Table 3).

Histological examination (Fig. 15) of the recipient–donor boundaries revealed the ongoing primary adhesion process, which prevents acute rejection as it is described in the Banff classification [13, 14].

Figure 15 shows the skin and the subcutaneous tissue, consisting of two fragments, separated by the wound.

The first fragment (recipient) is a skin flap with platysma. The skin is a set of ordinary layers with signs of keratinization and accompanying elements (hair follicles, sebaceous glands). Fatty tissue includes vessels of various sizes. Platysma is of the usual structure, it consists of longitudinal and transverse muscle fibers. In the deep layer, there are glandular structures.

The second fragment is the skin flap with platysma. The skin is a set of ordinary layers with signs of keratinization and accompanying elements (hair follicles, sebaceous glands). Fatty tissue includes vessels of various sizes. The typical platysma of longitudinal and transverse muscle fibers has narrow strands of granulation tissue penetrating it. The vessels contain form elements.

The wound is a narrow slit filled with granulation tissue of low cellularity. The granulation tissue mainly consists of small capillaries and interlayers of connective tissue with thin fibrils. It is practically not infiltrated with polymorphonuclear leukocytes (neutrophils), lymphocytes. They are found only in the surface layer under a patch of necrotic epidermis. Along the wound slit, infiltration with multinucleated cells can only be seen from the side of the first fragment.

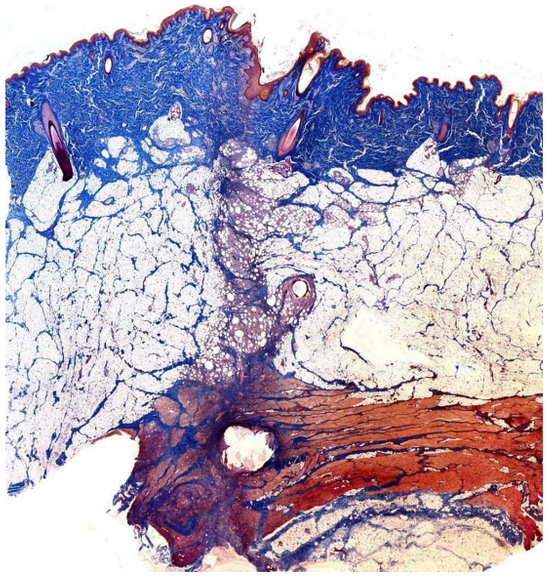

Fig. 15. Place of fusion of the flap with the recipient's tissues on the scanned image of the histological specimen

Table 4. Flap survival depending on the type of antibacterial and immunosuppressive therapy selected

Immunotherapy	Result
1st stage	
Antibacterial (ceftriaxone i.m. OD) + immunosuppressive therapy (prednisolone 120 mg or 240 mg as pulse therapy in case of rejection)	Two flaps (out of 10) from different pairs: survival without signs of acute rejection up to 36 days, development of delayed acute rejection followed by a pulse therapy relief attempt
2nd stage	
Antibacterial therapy (enrofloxacin i.m. OD) and immunotherapy (16 mg of dexamethasone i.m. OD, 32 mg of dexamethasone OD as pulse therapy in case of rejection)	Two flaps (out of 8) from different pairs — engraftment on the 21st day, with arrested acute rejection in the postoperative period
3rd stage	
Antibacterial therapy (lincomycin + spectinomycin i.m. OD) and immunotherapy (tacrolimus — intraoperative i.v., methylprednisolone i.m.)	Two flaps (out of 8) from different pairs — engraftment on the 14th day without signs of rejection

Table 4 shows the results of graft retention depending on the therapy regimens in the peri- and postoperative periods. It should be noted that the response is more effective in the cases where acute rejection reactions were purposefully relieved.

DISCUSSION

Even with the histological analysis confirming graft healing, it is necessary to closely observe the dynamics of the processes post-surgery and adjust the immunosuppressive therapy regimen with minimum possible delay following registration of signs of the acute tissue rejection reaction.

Having analyzed the results of our experiment and considered the cases of development of acute graft rejection, we concluded that it is necessary to continue development and testing of the immunosuppression regimen, which is consistent with the results other researchers have arrived at [15]. Another group of researchers has discovered that the features of the composite graft play a role in the development of rejection in one of its components [16], which leads to loss of the skin part of the flap while its muscle components remains.

Thus, the question is raised about the need to select objective methods for diagnosing the state of all components of the flap. Also, compared to single organ transplantation, surgeries involving composite grafts require greater attention to the specific features of such grafts.

CONCLUSIONS

The experimentally tested composite facial graft cross-transplantation technique allows all members of the team (surgeons, anesthesiologists, transplantologists, immunologists) to practice and improve their skills involved in the preparation, conduct of the surgery and postoperative rehabilitation of face transplant patients. Extended anesthetic aid was registered to decrease the operating time and improve survival rate of the subjects post-surgery.

The immunosuppressive therapy applied at this stage of the experiment requires further adjustment and testing to reduce the risk of development of acute or chronic rejection.

The emphasis on the unique features of composite grafts may allow additional, more specific treatment, which can multiply the life expectancy of patients with such grafts. Given the above, it is worth considering the possibility of using alemtuzumab perioperatively in addition to the plan typically followed in the context of transplantation surgeries.

References

1. Fu-Chan Wei, Mardini S. Flaps and Reconstructive Surgery. Elsevier, 2016; 872 p.
2. Pejpl AD, redaktor. Plasticheskaja i rekonstruktivnaja hirurgija lica. M.: Binom. Laboratorija znanij, 2007; 952 s. Russian.
3. Nerobeev AI, Plotnikov NA. Vosstanovitel'naja hirurgija mjagkih tkanej cheljustno-licevoj oblasti. M.: Medicina; 288 s. Russian.
4. Sosin M, Ceradini DJ, Levine JP, Hazen A, Staffenberg DA, Saadeh PB, et al. Total Face, Eyelids, Ears, Scalp, and Skeletal Subunit Transplant. Plastic and Reconstructive Surgery. 2016; 138 (1): 205–19.
5. Pomahac B, Diaz-Siso JR, Bueno EM. Evolution of indications for facial transplantation. Journal of Plastic, Reconstructive Aesthetic Surgery. 2011; 64 (11): 1410–6.
6. Wo L, Bueno E, Pomahac B. Facial transplantation. Current Opinion in Organ Transplantation. 2015; 1.
7. Iske J, Nian Y, Maenosono R. Maurer M, Sauer IM, Tullius SG. Composite tissue allotransplantation: opportunities and Challenges. Cellular Molecular Immunology. 2019; 16: 343–9
8. Siemionow M. The Know-How of Face Transplantation. L.: Springer-Verlag, 2011; 494 p.
9. Siemionow M. Plastic and Reconstructive Surgery Experimental Models and Research Designs. L.: Springer-Verlag, 2015; 661 p.
10. Karkishhenko NN, Grachev SV. Rukovodstvo po laboratornym zhivotnym i al'ternativnym modeljam v biomedicinskih issledovanijah. M.: Profil'-2C, 2010; 344 s. Russian.
11. Rukovodstvo po rabote s laboratornymi zhivotnymi dlja sotrudnikov GBOU VPO RNIMU im. N.I.Pirogova Minzdrava Rossii, zanjatyh provedeniem doklinicheskih ispytanij. M., 2015; 42 s. Russian.
12. Rifkin WJ, David JA, Plana NM, Kantar RS, Diaz-Siso JR, Gelb BE, et al. Achievements and Challenges in Facial Transplantation. Annals of Surgery. 2018; 268 (2): 260–70.
13. Solez K, Racusen LC. The Banff classification revisited. Kidney International. 2013; 83 (2): 201–06.
14. Schneider M, Cardones ARG, Selim MA, Cendales LC. Vascularized composite allotransplantation: a closer look at the banff working classification. Transplant International. 2016; 29 (6): 663–71.
15. Kueckelhaus M, Fischer S, Seyda M, Bueno EM, Aycart MA, Alhefzi M, et al. Vascularized composite allotransplantation: current standards and novel approaches to prevent acute rejection and chronic allograft deterioration. Transplant International. 2015; 29 (6): 655–62.
16. Sinha I, Pomahac B. Split rejection in vascularized composite allotransplantation. Eplasty. 2013; 13: e53.

Литература

1. Fu-Chan Wei, Mardini S. Flaps and Reconstructive Surgery. Elsevier, 2016; 872 p.
2. Пейпл А. Д., редактор. Пластическая и реконструктивная хирургия лица. М.: Бином. Лаборатория знаний, 2007; 952 с.
3. Неробеев А. И., Плотников Н. А. Восстановительная хирургия мягких тканей челюстно-лицевой области. М.: Медицина; 288 с.
4. Sosin M, Ceradini DJ, Levine JP, Hazen A, Staffenberg DA, Saadeh PB, et al. Total Face, Eyelids, Ears, Scalp, and Skeletal Subunit Transplant. Plastic and Reconstructive Surgery. 2016; 138 (1): 205–19.
5. Pomahac B, Diaz-Siso JR, Bueno EM. Evolution of indications for facial transplantation. Journal of Plastic, Reconstructive Aesthetic Surgery. 2011; 64 (11): 1410–6.
6. Wo L, Bueno E, Pomahac B. Facial transplantation. Current Opinion in Organ Transplantation. 2015; 1.
7. Iske J, Nian Y, Maenosono R. Maurer M, Sauer IM, Tullius SG. Composite tissue allotransplantation: opportunities and Challenges. Cellular Molecular Immunology. 2019; 16: 343–9
8. Siemionow M. The Know-How of Face Transplantation. L.: Springer-Verlag, 2011; 494 p.
9. Siemionow M. Plastic and Reconstructive Surgery Experimental Models and Research Designs. L.: Springer-Verlag, 2015; 661 p.
10. Каркищенко Н. Н., Грачев С. В. Руководство по лабораторным животным и альтернативным моделям в биомедицинских исследованиях. М.: Профиль-2С, 2010; 344 с.
11. Руководство по работе с лабораторными животными для сотрудников ГБОУ ВПО РНИМУ им. Н.И.Пирогова Минздрава России, занятых проведением доклинических испытаний. М., 2015; 42 с.
12. Rifkin WJ, David JA, Plana NM, Kantar RS, Diaz-Siso JR, Gelb BE, et al. Achievements and Challenges in Facial Transplantation. Annals of Surgery. 2018; 268 (2): 260–70.
13. Solez K, Racusen LC. The Banff classification revisited. Kidney International. 2013; 83 (2): 201–06.
14. Schneider M, Cardones ARG, Selim MA, Cendales LC. Vascularized composite allotransplantation: a closer look at the banff working classification. Transplant International. 2016; 29 (6): 663–71.
15. Kueckelhaus M, Fischer S, Seyda M, Bueno EM, Aycart MA, Alhefzi M, et al. Vascularized composite allotransplantation: current standards and novel approaches to prevent acute rejection and chronic allograft deterioration. Transplant International. 2015; 29 (6): 655–62.
16. Sinha I, Pomahac B. Split rejection in vascularized composite allotransplantation. Eplasty. 2013; 13: e53.