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The donor management algorithm in transplantation of a composite facial tissue allograft. First experience in Russia

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In the period from 2005 to December 2015, 37 transplantations of vascularized composite facial tissue allografts (VCAs) were performed in the world. A vascularized composite tissue allotransplantation has been recognized as a solid organ transplantation rather than a special kind of tissue transplantation. The recent classification of composite tissue allografts into the category of donor organs gave rise to a number of organizational, ethical, legal, technical, and economic problems.

In May 2015, the first successful transplantation of a composite facial tissue allograft was performed in Russia. The article describes our

experience of multiple team interactions at donor management stage when involved in the identification, conditioning, harvesting, and delivering donor organs to various hospitals.

A man, aged 51 years old, diagnosed with traumatic brain injury became a donor after the diagnosis of brain death had been made, his death had been ascertained, and the requested consent for organ donation had been obtained from relatives. At donor management stage, a tracheostomy was performed and a posthumous facial mask was molded.

The "face first, concurrent completion" algorithm was chosen for organ harvesting and facial VCA procurement; meanwhile, the facial allograft was procured as the "full face" category.

The total surgery duration from the incision to completing the procurement (including that of solid organs) made 8 hours 20 minutes. Immediately after the procurement, the facial VCA complex was sent to the St. Petersburg clinic by medical aircraft transportation, and was there transplanted 9 hours later. Donor kidneys were transported to Moscow by civil aviation and transplanted 17 and 20 hours later.

The authors believe that this clinical case report demonstrates the feasibility and safety of multiple harvesting of solid organs and a vascularized composite facial tissue allograft. However, this kind of surgery requires an essential multidisciplinary approach. Establishing of facial VCA transplantation Program is a complicated process for transplant centers and can hardly be implemented without a properly organized post-mortem organ donation system at a national level. Today these criteria are met only by the Coordination Center for Organ Donation at FMBA of Russia.

Keywords: facial tissue transplantation, multiorgan donor, coordination of organ donation, requested consent, organ harvesting for transplantation.

Introduction

Transplantation of vascularized composite tissue allografts (VCAs) denotes the transplantation of vascularized body parts (both in the anatomical, and functional sense) from the donor to the recipient containing several types of tissue: skin, muscles, bones, nerves, and blood vessels. The first successful transplantation of an upper limb was performed in 1998 in France [1]. In 2005, the first face tissue transplantation was performed in Lyon [2]. According to M. Sosin and E. Rodriguez, 37 facial VCA transplantations (20 partial and 17 complete ones) were performed worldwide from 2005 to December 2015 [3]. Initially, VCA transplantation was regarded as a specific kind of tissue transplant, but with the experience of such surgery, there came an understanding that the VCA transplantation was more consistent with a solid organ transplantation rather than the tissue transplant [4-9]. After a thorough evaluation involving the transplant community, the US Department of Health has recently published its decision recognizing VCA as a donor organ and has given the definition of VCA based on a number of criteria (Table. 1) [10]. An incomplete list of body parts that meet the definition of VCA, includes the limbs, face, larynx, abdominal wall, tongue, and esophagus [11, 12]. Similar trends regarding VCA categorization exist in Europe. [13]

The aim of the paper was to describe our experience in coordinating the interactions between different professional teams involved in the identifying, and conditioning the donor with a diagnosed brain death, that

was followed by multiorgan explantation of solid donor organs and facial VCA.

Table 1. Criteria to define VCA as a donor organ

• Vascularized part of the body that functions requiring the blood flow that can be restored by means of surgical vascular connections.
• Contains several types of tissues.
• Obtained from a donor as a functional or anatomical part of the body.
• Transplanted to the recipient as an anatomic or functional part of the body.
• Subjected to minimal processing during transplantation which does not alter the initial functional characteristics of the VCA.
• Is used to replace or to complete the homologous part of the recipient's body that would perform the same main function in the donor.
• Sensitive to ischemia; cryopreservation is impossible.
• Requires immunosuppression, there is the risk of rejection.

Clinical Case Report

(Material and Methods)

In 2013, the Ministry of Healthcare of the Russian Federation instructed the Federal Medical-Biological Agency (FMBA) of Russia to arrange an explantation of face soft tissues from a postmortem donor to provide a high-tech medical assistance to the serviceman injured while fulfilling the military duties. To achieve this goal, the FMBA of Russia

determined the following objectives to organize the donation of a facial VCA:

I. Preparation of the legal and regulatory framework governing a facial VCA donation was identified. The legal basis for the explantation of the facial VCA included the following: Federal Law of 21.11.2011 No.323-FZ "On the fundamentals of health protection in the Russian Federation"; RF Law of 22.12.1992 No. 4180-1 "On the transplantation of human organs and(or) tissues"; Federal Law of 04.05.2011 No. 99-FZ "On licensing certain types of activity"; the RF Government Decree of 16.04.2012 No. 291 "On licensing the medical activities (except for specified activities carried out by medical organizations and other organizations within the private healthcare system, on the territory of Skolkovo Innovation Center)", the RF Ministry of Healthcare Order of 31.10.2012 No. 567-n "On approval of the procedure for rendering health care in the field of surgery (transplantation of human organs and (or) tissues)"; the RF Ministry of Healthcare and the Russian Academy of Medical Sciences (RAMS) Order of 25.05.2007 No. 357/40 "On approval of the List of human organs and(or) tissues accepted as transplantation objects, the List of healthcare facilities authorized to perform human organ and(or) tissue transplantation, and the List of healthcare facilities authorized to harvesting and procurement of human organs and(or) tissues", the permit from the RF Ministry of Healthcare authorizing the A.I.Burnasyan Federal Medical Biophysical Center of FMBA (Coordination Center for Organ Donation at FMBA of Russia) to procure a facial VCA from a posthumous donor for the purpose of its transplantation to recipient N.I.Egorkin; a requested consent to facial VCA explantation.

II. The organizational activities of the Coordination Center for Organ Donation at FMBA of Russia aimed at facial VCA explantation include:

1. Defining the criteria of a potential facial VCA donor.

A potential donor should meet the following criteria:

• Personally identifiable;

• Diagnosed brain death;

• Age 18-50 years;

• Gender: preferably a male;

• No damage to the facial skeleton;

• No skin diseases (acne, psoriasis, etc.), pyo-septic process in the area of intended surgery, and in the ear, nose, and throat (ENT) organs;

• External and common carotid arteries free from atherosclerosis;

• Being on the ventilator support for no more than 96 hours;

• Hemodynamically stable;

• Fit to the recipient's anthropometric data.

2. The immunologic work up of the recipient and the donor (blood group, the recipient's immune sensitization degree, the recipient's phenotype, the donor's phenotype, cross-matching) performed in the Immunology Laboratory of A.I.Burnasyan Federal Medical Biophysical Center of FMBA, Russia.

3. Donor testing for markers of infectious diseases (human immunodeficiency virus [HIV], syphilis, hepatitis B and C, Cytomegalovirus [CMV]).

4. Defining the specific requirements of conditioning the potential facial VCA donor before and during the explantation

5. Options and stages of the explantation of facial VCA and solid organs.

6. Transportation of procured facial VCA and solid organs within a limited time.

7. Coordinating all the involved services: the organ donation team, the surgical team of the Transplantation Center (in the Military Medical Academy named after S.M. Kirov), the Administration of the medical facility (the donor base), forensic medicine expert assessment, the prosecutor's office, the immunological service, the diagnostic laboratory for infectious diseases, the medical ground and air transportation teams, the document preparation and handling (Fig. 1).

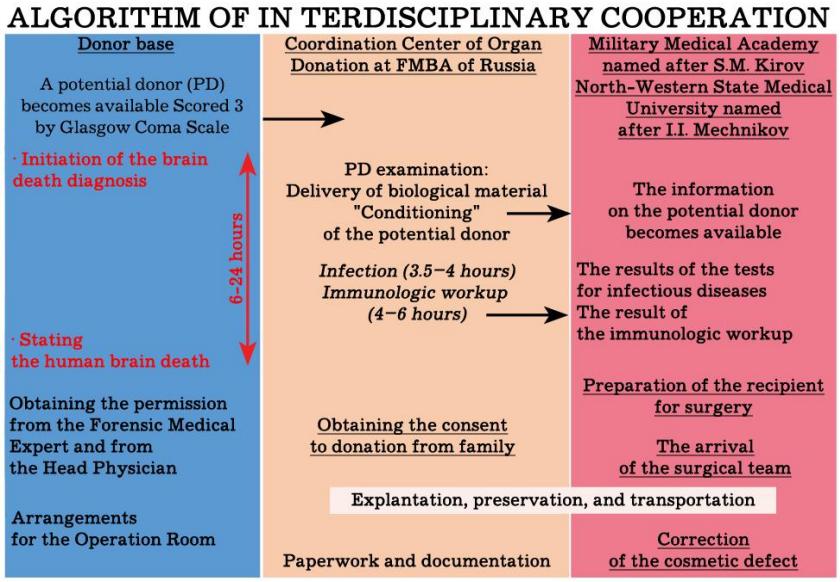

Fig. 1. Algorithm of interdisciplinary cooperation

III. The correction of the cosmetic defect on the donor's face after VCA explantation.

In May 2015, the Coordination Center of Organ Donation at FMBA of Russia received the information from the medical facility transplant coordinator reporting on an available potential donor with a brain injury in whom the procedure of ascertaining the brain death diagnosis had been initiated. The laboratory instrumental tests and immunological study found

no contraindications to the explantation of facial soft tissues. After the brain death diagnosis had been formally ascertained, the employees of the Coordination Center of Organ Donation at FMBA of Russia, in cooperation with the physicians of the medical facility managing the potential donor, obtained the donor's family consent to the donation of solid organs first, and of the facial soft tissue, later on. The forensic medical expert's report was issued with notification of the Prosecutor's Office and the Head of the medical facility prior to starting the explantation procedure.

The donor was the male of 51 years with blood group A(II) Rh+ diagnosed with an open brain traumatic injury, a severe brain contusion, subdural hematoma (250 mL) of the left temporal area, the brain edema and dislocation; post-craniotomy status of the left temporal region.

After the brain death had been ascertained, besides measurements of the general clinical laboratory parameters, he was assessed as a potential donor on the following plan:

• Blood tests for infectious disease markers (HIV, hepatitis B and C, syphilis, CMV);

• Donor's phenotype identification: A, B, Dr;

• CrossMatch testing;

• Cultures of oral content, nasopharynx and trachea contents for microflora and its sensitivity to antibiotics;

• X-ray of facial bones in two views and a computed tomography (CT) of facial bones;

• Doppler study of the major blood vessels of the neck and the facial vessels;

• The blood sample was taken to prepare a genetic passport in order to avoid possible errors in the identification of potential donor.

The potential donor management for 24 hours included: the hemodynamics stabilization, the blood oxygen-delivery function improvement, corrections of fluid and electrolyte imbalance, the control of hyperglycemia, polyuria, hypothermia, hormonal disturbances using a fluid therapy and a hormone replacement therapy (with methylprednisolone, insulin, Minirin), the choice of appropriate ventilation modes, the controlled warming of the potential donor. The oral cavity, nose, throat, and upper respiratory tract were regularly cleansed to prevent local and systemic septic contamination. The antibacterial therapy included carbapenems, fluoroquinolones, and antifungals.

By the time of surgery the hemodynamics had been stabilized, the aggressive cardiotropic support had been decreased, the diuresis rate had been reduced, hypernatremia and hypothermia had been corrected (Table. 2). While preparing the donor for surgery, the tracheostomy was performed and the postmortem silicone mask was molded (Fig. 2). Considering the field of surgery, the jugular vein and the radial artery were de-cannulated, and the femoral artery and vein were cannulated to ensure a convenient vascular access and a hemodynamics control.

Table 2. Changes in hemodynamics and main homeostasis parameters in a diagnosed brain-dead donor during donor management stage

Parameter	Before conditioning	Before explantation
Heart rate, beats/min	130	72
Blood pressure, mm Hg	100/70	115/65

Central venous pressure, cm H_2O	–2	+5
Temperature, °C	33.8	36.8
Diuresis rate, ml/h	1000	150
Dopamine dose, mg/kg/min	25	—
Norepinephrine dose, ng/kg/min	—	100
Hb, g/L	111	107
Ht, %	32	31
WBC, 10^9/L	9.0	7.0
PLT, 10^9/L	90	195
Total protein, g/L	63.4	58.1
Urea, mmol/L	3.0	3.9
Creatinine, mmol/L	168	139
Total bilirubin, mmol/L	22.6	17,5
Glucose, mmol/L	5.45	8,4
Aspartate aminotransferase, U/L	124	102
Alanine aminotranspherase, U/L	60	51

Lactate dehydrogenase, U/L	312	263
K^+, mmol/L	4.13	4.2
Na^+, mmol/L	168	154

Note: WBC, white blood cells in a complete blood count; PLT, platelets in a complete blood count.

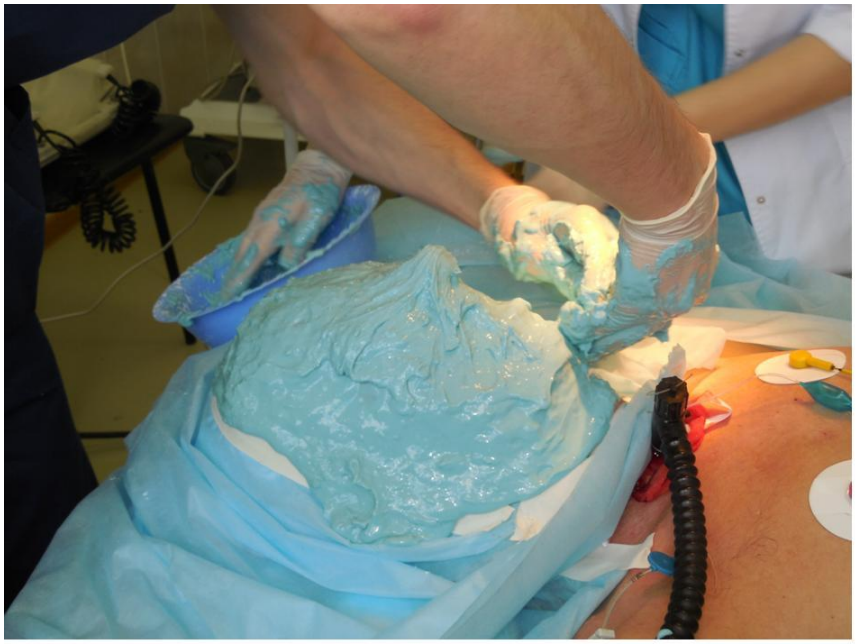

Fig. 2. Molding the donor's postmortem mask

The "face first, concurrent completion" algorithm was chosen for organ harvesting and facial VCA procurement; meanwhile, the facial allograft was procured as the "full face" category. [14, 15].

The total surgery duration from the incision to completing the procurement (including that of solid organs) made 8 hours 20 minutes.

Immediately after the procurement, the facial VCA complex was sent to St. Petersburg clinic by medical aircraft transportation, and was there transplanted 9 hours later. Donor kidneys were transported to Moscow by civil aviation and transplanted 17 and 20 hours later.

Discussion

The recent classification of VCA into the category of donor organs has created a number of organizational, ethical, legal, technical and economic problems [16]. The search for a suitable donor for facial VCA transplantation can take an indefinite amount of time. This is determined not only by the need of the phenotype data compatibility, but also by the certain requirements for age, sex, skin color, anthropometric data, as well as by the need in obtaining the deceased person's family consent to VCA explantation. The system coordinating the organ donation in the Russian Federation lacks an inter-regional cooperation between the coordination centers, it is far from perfect and provides no chance to solve this problem at a one-region level. Therefore, the task of finding a potential facial VCA donor was set for the FMBA of Russia.

The FMBA of Russia Coordination System of postmortem human organ and/or tissue donation consists of 3 levels:

• The 1st level includes the Transplant Coordinator of the medical organization within the jurisdiction of the FMBA of Russia;

• The 2nd level comprises the system of regional FMBA Organ Donation Coordination Centers in Russia;

• The 3rd level is the Coordination Center for Organ Donation at FMBA of Russia.

Three regional FMBA Organ Donation Coordination Centers in Russia were involved in the search for a suitable facial VCA donor. The information on potential donors came to the Coordination Center for Organ Donation at FMBA of Russia from more than 30 donor hospital departments in a 24-hour mode. After 9 months, a suitable donor was found.

Although VCA became classified as a donor organ, currently existing registers or donor cards in any country do not include items on the consent to a facial VCA donation or waiver. This requires an appropriate adaptation of documentation and the approaches to talking to the family, as VCA harvesting demands a separate explicit consent, even in the countries where a presumed consent to organ donation is stipulated by the law. At the same time, the procedure of obtaining the consent to VCA donation, especially the facial VCA, should not impede the process of other organ donation, so the consent to VCA donation is advisable to be asked for only after the consent for the donation of other organs has been obtained, and only in thoroughly selected cases. So, the initially taken decision implied: should a potential donor be found and identified as suitable by clinical, immunological and anthropometric parameters, the procedure of obtaining the requested family consent to organ donation first and then to a facial VCA donation would be started. In the period of donor selection, the families of 3 deceased individuals consented to the donation of solid organs, but were strongly against the facial VCA donation.

There is another set of problems that relate to the donor identification and selection. VCA transplantation, as a rule, is not a life-saving surgery, so a careful selection of donors is crucial to prevent any adverse events (a VCA injury, a mismatch of morphometric parameters, poor vascular status). Generally, we can say that the basic principle "the organ looking for a recipient "underlying the distribution of solid organs, in the case of VCA transplant changes into the principle "the recipient looking for a VCA".

The main group of problems refers to the coordination during the surgical procedure for donor organ explantation. By analogy with the procedure of obtaining the consent for VCA donation that must not

adversely affect the solid organ donation, so the VCA explantation should not affect the removal of other donor organs. Based on the laboratory and instrumental test results in our case, we considered the donor as a potential multiorgan donor of liver, kidneys, and facial VCA.

The facial VCA mobilization from a brain-death-diagnosed donor bears a unique set of challenges compared to the mobilization of solid organs and limb VCAs. A great number of medical and surgical staff may be engaged in the multiorgan harvesting procedure: up to 30, including 13 surgeons [17]. In our case, the procedure was performed with the participation of 1 plastic surgeon, 1 cardiovascular surgeon, 1 surgeon assistant, 3 abdominal surgeons, 2 anesthetists, and 4 surgical nurses. The identification, and mobilization of several vessels, nerves, muscles, and bone structures in situ might take from 7 to 12 hours, up to 22 hours in some cases [16-18]. This creates a high risk of massive blood loss (5-7 liters), and severe hypothermia [19-21] that can be fatal for the solid organ. Moreover, the surgery duration creates a large workload on operating teams, especially if they arrived from other regions.

A well-structured plan of making the procedure is crucial. Temporary and logistics requirements used when coordinating the solid organ donation are hardly well-known to surgeons, while the solid organ procurement teams are largely well accustomed to strictly regulated organ harvesting/recovery procedures.

Despite a limited world experience of the multiorgan explantation of donor solid organs and facial VCA, 3 relatively structured protocols of such procedures have been formed in practice. All the protocols consider primarily the donor's status, namely the hemodynamic stability, and determine the starting point of obtaining the thoracoabdominal access.

Despite the impossibility to detail a standard technique, the modern literature recognizes the need for a coordinating algorithm defining the work of each team in the context of donor's condition [22].

The first approach involves a preventive thoracoabdominal access prior to starting the facial VCA detachment in extremely unstable donors with severe hemodynamic impairments and coagulopathy. This approach implies a simultaneously performed cannulation of intrathoracic organ vessels, the blood vessels going to the facial VCA through the aortic arch, the abdominal cavity vessels. A total heparinization, perfusion, and explantation of solid organs are performed. Further, the VCA mobilization shall be made on a cooled non-heart-beating donor.

The second approach involves setting a so-called donor physiological threshold agreed upon between the surgeons and anesthesiologists (any set of pre-approved parameters: the blood pressure, diuresis rate, blood loss volume, vasopressor and cardiotonics infusion rates, etc.). Primarily, the facial VCA mobilization is performed ("face first" principle), and only in case the donor parameters run beyond the physiological threshold, the thoracolaparotomy is performed. This approach obviates the need of a preventive thoracolaparotomy and reduces the cold ischemia time for the facial VCA.

The third option, being considered the optimal one, implies the starting time of solid organ mobilization to be at approximately 60 minutes before the expected facial VCA explantation. This approach is called "face first, concurrent completion" and is preferable in a stable donor who is not expected for an entire face explantation, and in whom the mobilization of solid organs does not take much time. The prior mobilization of facial VCA can preserve its perfusion, but potentially endangers the donor's condition

because of the surgery duration and blood loss. Therefore, an intraoperative mobilization of the facial VCA vascular pedicle increases the safety in the event of donor's inability. The vessels can be rapidly cannulated for cold perfusion without a long and potentially dangerous thoracic access [17].

Regardless of the chosen strategy in each case, one should remember the main purpose that is to prevent the loss of solid organs.

Of course, the algorithm of surgery may depend on time preferences of donor operating teams. Time limits may be considerably amended by the requirements of the transplantation teams who have to make operations on the recipient at several hours before the organ procurement. But it is very important not to exceed "the point of no return", thus avoiding an unnecessarily prolonged operation on the donor, and reducing the time of cold ischemia.

In our case, the "face first, concurrent completion" tactics was jointly chosen with prior mobilization of facial VCA vascular pedicle (Fig. 3). The preoperatively made tracheostomy and molding of posthumous donor facial silicone mask reduced the total time of harvesting the donor organs, and lessened the workload on the team.

Immediately before the donor surgery, the "donor's physiological threshold" was defined. That implied that the drop in systolic arterial pressure below 80 mm Hg uncorrectable by the increased cardiotonic support and infusion rate; the reduced hemoglobin level below 70 g/L; and the body temperature below 33 °C should be considered the indications to perform laparotomy, to isolate the aorta and the inferior vena cava, and to cannulate vessels for the purpose of abdominal organ preservation in situ.

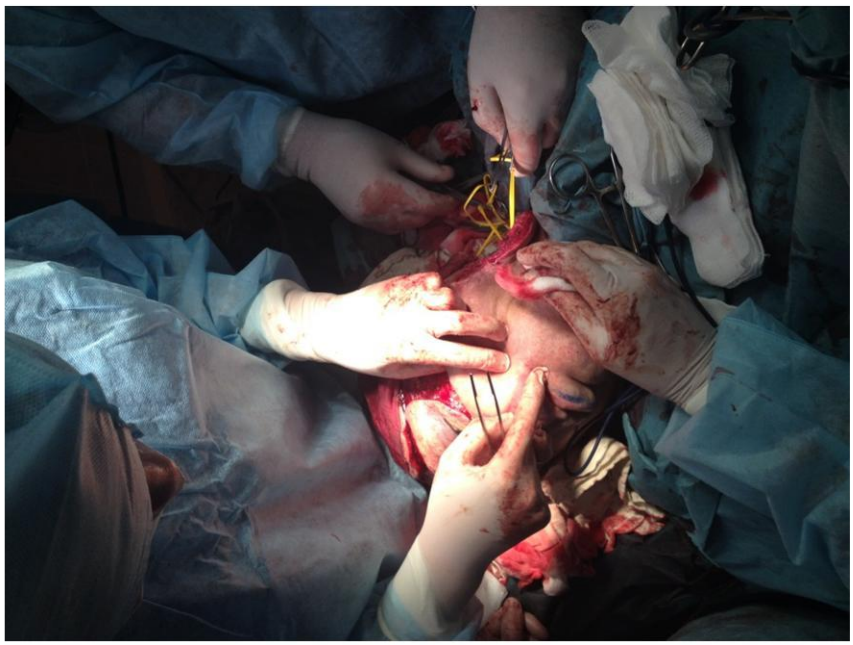

Fig. 3. Preparation of the facial VCA major vessels for cannulation

Total surgery duration was 8 hours and 20 minutes. The facial VCA detachment stage took 7 hours and 15 minutes. At 60 minutes before completing the facial VCA mobilization, the abdominal surgery team started abdominal organ retrieval. After the aorta and inferior vena cava had been prepared and the kidneys and liver had been isolated, a simultaneous cannulation of the aorta, the inferior vena cava was performed from the side of abdominal cavity and the common carotid arteries. The retrieved abdominal organs, and the facial VCA were preserved simultaneously using the *Custodiol* solution, 15 liters, and 5 liters, respectively (Fig.4, 5).

Despite a significant excess of the estimated surgery duration, a considerable blood loss (2 liters), the need to increase the cardiotropic support, and the presence of hypothermia of 33.5 °C, we managed to keep the donor under the "physiological threshold." As mentioned above, no transfusion of blood products was performed. That was primarily reasoned

by the need to follow the legal provisions not allowing blood transfusions in corpses.

Fig. 4. Preservation of facial VCA by flushing carotid arteries with Custodiol solution

Fig. 5. The facial VCA after explantation

Logistics

The facial VCA donation has been considered a difficult task for the clinics and medical centres different from those which perform a facial VCA explantation. According to Brazio et al., currently the logistics requirements for the implementation of multiorgan donor retrievals of solid organs and facial VCA under the scheme "face first, concurrent completion" are too complicated; at least, there has been no such case described in scientific literature [18]. It is explained predominantly by the lack of experience and knowledge, insufficient time of a facial VCA tolerability to cold ischemia, particularly that of the muscle tissue [23, 24]. Considering the results of upper limb transplantation, a 4-hour period of cold ischemia could be well tolerated [16].

In our case, the facial VCA had to be transported at a distance of 1000 km. The task could be performed by the aviation service of the Russian Federation Ministry of Defence. Given that the donor liver and kidney had to be transported to the distance over 500 km by the civil aviation, no scheduled flights at the nearest time made us to refrain from donor liver explantation, so only the kidneys were procured.

Conclusion

Our case report has demonstrated the feasibility and success of multiorgan explantation of solid organs and vascularized facial tissue allograft. However, such operations require a proper multidisciplinary approach. Establishing a facial VCA transplantation programme is a complex process for transplant centers, and the task can not be solved without an appropriate post-mortem organ donation system at a national

level. For the success of this program, the following conditions must be created:

• Establishment of a working system coordinating the organ donation, the system that would unite all the regions of the Russian Federation. Particularly important aspects for the program implementation include the creation of a functioning center that would coordinate the organ donation at all stages starting from a potential donor identification, evaluation, management and obtaining the family consent for donation of solid organs and facial VCA, notifying all specialists (teams) to be involved in the process, and coordinating their further activities, and finally, keeping a uniform waiting list of facial VCA recipients. At the same time, the Coordination Center for Organ Donation should have all appropriate logistics and technical equipment including extracorporeal membrane oxygenation devices, devices for normothermic perfusion of explanted organs, ambulance cars and air transport. Today these criteria are met only by the Coordination Center for Organ Donation at FMBA of Russia.

• The staff and close cooperation of organ donation coordinator teams with the surgical teams who perform organ explantation, and those who subsequently transplant the facial VCA are the keys to success. Refining the interactions between various services, health organizations, and even regulatory authorities require regular training and exercises.

• Public awareness about all aspects of organ donation and transplantation of solid organs and facial VCAs, as well as the willingness to post-mortem facial tissue donation are the most important prerequisites for the expansion the of facial VCA donor pool.

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