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Face Transplantation: Medical Considerations

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Abstract Face transplantation has been performed in 37 patients worldwide. To provide excellent outcomes, it is important to understand the medical considerations that are present in every aspect of this procedure. Pre-operative medical considerations are largely related to patient selection, intra-operative considerations are related to anesthesia, and post-operative considerations include complications and treatment of adverse effects of immunosuppression. This paper will discuss each area in more detail.

Keywords Face transplantation · Medical considerations

Introduction

Facial transplantation is now a realistic option for selected patients with severely deformed faces. In the USA, these procedures are performed under clinical trials as face transplantation is not standard of care. To date, 37 patients have undergone facial transplantation at multiple different institutions around the world [1••]. Their facial deformities resulted from either trauma due to animal bites, burns, falls, machine accidents, ballistic injury, or congenital malformations such as neurofibromatosis [1••, 2]. Severe facial deformities are unique in their complexity due to the variety of tissues present within an anatomic region, making conventional reconstruction challenging. The use of vascularized composite allotransplants allows the possibility of simultaneously reconstructing each different tissue. Donor allografts have contained skin, soft tissue, nose, lips, chin, cheeks, eyelids, lacrimal glands and ducts, infraorbital floor, lateral orbital wall, zygoma, maxilla with teeth, palate, mandible, parotid glands with ducts, tongue, intra-oral mucosa, ears, forehead, and/or scalp [1••, 2–3]. Survival of each of these tissues that comprise what has been described as the facial organ has been shown to be dependent on a single arterial and venous anastomosis [4]. However, two anastomoses are almost universally used with preferred recipient and donor arteries being external carotid, facial or maxillary, and preferred veins being external jugular, facial, or thyrolinguofacial trunk [2]. Branches of facial nerves are repaired, as are identifiable sensory nerves [2]. Outcomes include return of sensation, return of facial functions including eating, breathing, drinking, expressing or communicating, and improved esthetics [5].

While technical considerations are important, medical considerations in the pre-operative, intra-operative, and post-operative phases of face transplantation are equally significant.

Pre-Operative Medical Considerations

Patient selection is the most critical factor in face transplantation and must involve a multidisciplinary approach including plastic surgery, transplant medicine, psychiatry, social work, radiology, infectious disease, and rehabilitation among others. In contrast to other solid organs for end-stage diseases, candidates for face transplantation are usually healthy. General health screening often includes lab work and imaging (Table 1) [6]. Results of

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Table 1 Pre-operative screening tests [6, 7]

Lab tests	Imaging	Other
Complete chemistry	Maxillofacial computed tomography with three-dimensional formatting	Cardiac stress test
Fasting lipids	Chest radiography	Colonoscopy
Renal panel	Head and neck computed tomography angiography	Stool hemoccult (Beckman Coulter, Brea, Calif)
Liver function tests	Echocardiography	Purified protein derivative
Parathyroid hormone		Pap test (female)
Complete blood count		Mammogram (female)
Prothrombin time/partial thromboplastin time/international normalized ration		
Prostate-specific antigen		
Hepatitis B surface antigen hepatitis B core antibody		
Hepatitis C antibody		
Cytomegalovirus screening		
Epstein-Barr virus screening		
Varicella zoster virus		
Rapid plasma regain		
Human immunodeficiency virus		
Panel reactive antibody		
HLA typing		
ABO type		

testing as well as a physical exam are used to assess whether a patient is a good medical candidate for face transplantation. Generally, patients have been between ages 18 and 60 and have a minimal coexisting medical illness or trauma, with all pertinent organ systems within normal limits [7]. Absolute medical contraindications for face transplantation in most clinical trials include record of poor medical compliance, current pregnancy, American Society of Anesthesiologists class 5, end-stage organ disease, acquired immunodeficiency syndrome or chronically immunosuppressed, active cancer excluding non-melanoma skin cancer, significant psychiatric disorder history, or documented history of previous suicide attempt [7]. Relative contraindications include active smoker, active bacterial, viral or fungal infection, active hepatitis C infection, positive CMV donor with a negative recipient, alcohol or drug abuse history, type 1 diabetes mellitus, connective tissue disorder, ASA class 4, younger than 18 or older than 60, significant critical organ disease, or remote history of carcinoma [7].

Given the necessity of lifelong immunosuppression, prior malignancy is considered an absolute contraindication for face transplant by many. One transplant done after treatment for head and neck cancer recurred 4 years post-operatively. This eventually led to her death [3]. Others consider cancer patients in remission over 5 years and will therefore consider those greater than 5 years from cancer treatment as possible candidates [5].

Whether a CMV negative recipient should receive a transplant from a CMV positive donor has been a topic of debate. Patients who developed CMV viremia after transplant were all seronegative patients who received seropositive transplants [8•]. However, most of these episodes did not correlate with rejection and all patients were successfully treated with valganciclovir, foscarnet, or investigational CMX001 treatment [8•, 9]. One report noted in the literature describes an episode of rejection that correlated with onset of valganciclovir-resistant CMV viremia [10]. Strategies have been proposed to decrease risk of CMV viremia post-transplantation. Similar to other organ transplants, strategies to address CMV mismatch include frequent monitoring and extension of prophylactic antiviral medications [8•].

While most would consider HIV positive status an absolute contraindication to face transplantation, there is one report of such a case in the literature [11, 12•]. The recipient was on HAART (ritonavir, darunavir, raltegravir, etravirine, and enfuvirtide), had CD4 counts over 400/ml, and had a negative viral load [11]. Proponents of this case cite the success of solid organ transplants in HIV-positive individuals with CD4 counts greater than 200/ml and negative viral loads [11].

Blindness has been debated as possible exclusion criteria. Some believe that visual feedback is necessary to participate in physical therapy, to monitor for rejection, that blind patients cannot appreciate the cosmetic outcome of transplantation, and that they cannot perceive social reactions to their injuries therefore there is no need to use such a scarce resource on these patients [13]. However, in the face transplants that have been performed to date, 13 % of patients have been blind, and reports show these patients have at least equal outcomes, if not better, when compared to patients with sight [3, 13]. In this population, physical therapists utilize non-visual feedback mechanisms and blind patients have gained the same function as those with sight, allowing for independent activities of daily living [13]. Rejection in this population has been monitored by the patients' support system and by frequent follow-up [13]. Additionally, research on other topics including eating disorders and cosmetic surgery such as breast augmentation has shown that vision is not necessary to develop the social effects of deformity nor is it necessary to obtain the benefit of improvement of the deformity [13].

A thorough psychological evaluation cannot be overemphasized. Candidates for transplantation must understand the procedure and alternatives and have realistic expectations [14]. They must be able to handle the stress and challenges that come with face transplantation, be willing to comply with lifelong immunosuppression, and adapt to a changed appearance [14]. While some believe face transplantation may create identity issues, the literature reveals patients feel they have conserved their own identities [15]. Additionally, it is important to identify any patients with a history of psychoses, depression, substance abuse, and severe personality disorder

as these patients may need additional treatment prior to being considered a candidate for face transplantation [6]. While previously mentioned as an absolute contraindication to face transplantation, self-injury is currently an area of debate. Some believe these patients can now be considered candidates as long as they are cleared by psychology [5].

Although not a medical consideration per se, appropriate social and financial support is imperative for any face transplant patient and deserves brief mention, especially considering the cost of lifelong immunosuppression. Without these resources in place, disqualification is almost a certainty in many centers. Many programs list inability to have reliable follow-up or reliably obtain immunosuppression medications as exclusion criteria in their trials. Screening and clearance by social work is included in the pre-operative evaluation of these patients [12•].

Intra-Operative Medical Considerations

The surgical procedure is extensive and long, oftentimes taking between 15 to 25 h [3]; therefore, planning is important regarding anesthetic agent, fluid management, and use of vasopressors. The anesthetic agent used may have an effect on the face transplant survival. Sevofluorane has been shown to protect the endothelium from ischemia-reperfusion injury and promotes vascular healing [16, 17]. Additionally, sevofluorane may help prevent edema by decreasing the extravasation of plasma into the interstitial space [18]. Fluid management has been shown to affect post-operative complications. A study of 354 free flaps for breast reconstruction reported that on multivariate analysis, the extremes of crystalloid infusion rate significantly predicted post-operative complications [19]. Studies examining the use of vasopressors in free-flap reconstruction have shown no correlation with flap loss or reoperation to vasopressor use. One retrospective study of 496 free tissue transfers for head and neck reconstruction showed no increase in major flap complications including complete failure, partial failure, or operative take back for a vascular complication in those patients that received vasopressors phenylephrine and/or ephedrine versus those that did not [20]. Another study examining 158 abdominally based free flaps for breast reconstruction showed no difference in complications among patients who receive vasopressors and those that did not [21]. However, close communication between anesthesia and the surgical team is paramount, especially when considering strategies to maintain hemodynamic status during surgery. Any use of vasopressors should be discussed with the surgical team prior to initiation.

In the microvascular reconstruction literature, reports are conflicting whether hypothermia is beneficial or harmful to free flaps [22]. An animal study evaluating flap survival in rats showed the highest flap survival 95 %, in the group with core temperature of 34 °C, compared to those at 35, 37, and 39 °C [23]. However, another animal study showed decreased blood flow through flaps in rats with colder core temperatures [24]. While this literature is conflicting regarding flap survival, hypothermia has also been shown to increase surgical site infections post-operatively [25].

Careful monitoring of patients is essential. Use of a femoral central line is most commonly used, as this location is away from the head and neck region. Arterial lines are used for hemodynamic monitoring, as these procedures can have massive blood loss. One study of five face transplantations reported an average infusion of 22.7 packed red blood cells (range 9 to 60), 19.8 fresh frozen plasma (range 2 to 60), and 13.7 platelets (0 to 54) [18].

Post-Operative Medical Considerations

The most significant post-operative medical considerations are those that are caused by immunosuppression. In most centers, immunosuppression regimens are commonly triple therapy consisting of an antimetabolite (mycophenolate mofetil), a calcineurin inhibitor (tacrolimus), and steroids [3]. Induction using antithymocyte globulin has been used in almost all cases [3].

Frequent follow-up is necessary to screen for malignancy, infection, or metabolic changes that can accompany immunosuppression. For solid organ transplant recipients, the risk of basal cell carcinoma is 10–16 times higher than the general population, and the risk for squamous cell carcinoma is 65–250 times higher [26]. Skin malignancy has been seen in the face transplant population. One patient reported in the literature developed HPV+ cervical carcinoma in situ at 4 years post-transplantation and nodular-pigmented basal cell carcinoma on the face 6 years after transplantation. The cervical carcinoma in situ was treated with conization and the basal cell was treated with excision [26]. Another face transplant recipient developed two squamous cell carcinomas of the foot and hand in the first year after transplantation. This patient also developed lymphoma that was successfully treated [26].

Similar to other organ transplant recipients, patients after face transplantation are placed on antibiotic prophylaxis [8•, 27]. Post-face transplant infectious complications reported in the literature include viral, bacterial, and fungal. Viral infections include cytomegalovirus (CMV), herpes simplex virus (HSV), herpes zoster, and Epstein-Barr virus (EBV) [3, 8•, 28]. Fungal infections include Majocchi's granuloma, *Candida* stomatitis, and *Candida* surgical-site infections [8•]. Bacterial infections include *Enterobacter cloacae* bacteremia, *Pseudomonas Aeruginosa* pneumonia, *Pseudomonas Aeruginosa* surgical-site infection, *C. Difficle* and *Aeromonas* diarrhea, *Heamophilus influenza* pneumonia, tracheobronchitis, *Acinetobacter baumannii* surgical-site infection, and *Pseudomonas*- and *Staphylococcus epidermidis*-related blood stream infections [3, 8•, 27, 29]. Late infectious complications, beyond 6 months, include reactivation of HSV, molluscum contagiosum, bacterial conjunctivitis, viral gastroenteritis, CMV, and *C. difficile*-associated diarrhea [8•, 28, 29]. Parotitis and superinfected sialocele have also been observed

and were a result of anatomic aspects of the donor face that was transplanted [8•].

As with other transplants, routine testing and close follow-up is key to early diagnosis and treatment of metabolic complications of immunosuppression. Those reported in the literature include chronic renal insufficiency, new onset diabetes, and gastrointestinal side effects [3].

Regarding face transplantation, almost every patient has had at least one episode of acute rejection within the first few years after transplantation [1••, 3]. These acute episodes have been reversed with modulation of immunosuppression medications including those steroid resistant [30]. Two cases of chronic rejection have been reported in face transplantation [31]. One of these cases was caused by a decrease in immunosuppression medications due to EBV-induced lymphoma and hepatic EBV-associated post-transplant smooth muscle tumor requiring chemotherapy [31]. Graft versus host disease has not been reported in face transplantation [3].

Summary

Face transplantation has been performed in 37 patients worldwide. Medical considerations are present in every aspect of this procedure. Pre-operative medical considerations are largely related to patient selection. Intra-operatively, anesthetic considerations are important. Complications and treatment of adverse effects of immunosuppression are most common post-operatively.

Compliance with Ethical Standards

Conflict of Interest Michelle Coriddi and Jeffrey Janis declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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