

Facial Transplantation and Immunosuppressed Patients: A New Frontier in Reconstructive Surgery

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Composite tissue transplantation in reconstructing complex facial defects has developed tremendous interest over the recent years, since the first report of partial face transplantation performed in France in 2005. However, the controversy over the ethical, immunological, and psychological issues remains. Recently, we obtained IRB approval to perform partial face transplantation at Brigham & Women's Hospital, Boston. Here we present the rationale and IRB application process of our unique approach to this highly controversial procedure, which focuses on partial face transplantation on patients currently on immunosuppressants due to previous transplanted organ. 'Patient selection criteria', selection process, technical and immunological protocols are discussed. We currently share the concern that life-long immunosuppression associated with facial transplantation may not outweigh its benefits as compared to the alternative reconstructive methods. We asked ourselves the question of which patient population would risk less and overall benefit more from undergoing face transplantation, and identified those currently on immunosuppressive therapy the most suitable candidates. Organ transplant recipients are at increased risk of malignancy, particularly skin cancer commonly located in the facial region, necessitating surgical resection and facial reconstruction. They also have to take immunosuppressants to prevent rejection of their primary transplanted organ, which will minimize the need for additional immunosuppression associated with facial allograft. Being a previous organ recipient also diminishes the difficulty of complying with the strict postoperative immunosuppressive regimen, commonly encountered by organ transplant recipients. This approach could be very beneficial for previously immunosuppressed patients and perhaps take its place in our reconstructive ladder options.

Keywords: Face transplantation, Composite tissue, Immunosuppressed patients, Organ transplant recipients.

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Composite tissue transplantation is a clinical reality. Since the first successful kidney transplant by Dr. Joseph Murray at Brigham and Women's Hospital (1), the evolution of the field has led to successful transplantation of heart, lung, liver, bowel, pancreas, and pancreatic islet cells. In addition to life-saving organ transplants, composite tissue transplantation of extremities and more recently the face has also been performed. Facial transplantation has garnered tremendous interest over recent years since the first reported case in France in 2005 (2) followed by China and fuelled by reports in popular media. However, the controversy over the ethical, immunological, and psychological issues remains. Recently, we obtained IRB approval to perform facial allograft transplantation at Brigham and Women's Hospital, Boston, United States. Here, we present our unique approach toward

facial transplantation research that focuses on partial face transplantation in patients currently on immunosuppressive therapy for a previously transplanted organ. The rationale and the IRB application process are discussed. We believe that this technique could be very beneficial for previously immunosuppressed patients and perhaps take its place in our reconstructive ladder options.

Developing the Protocol

We developed our protocol in light of Guiding Principles published by American Society of Plastic Surgeons (ASPS) and American Society of Reconstructive Microsurgery (ASRM) in January 2006 (3). We agree with the ASRM and ASPS position paper in considering face transplantation an experimental procedure, and believe that "incremental steps are necessary to ensure its appropriate application." Here, we present the steps we will take to maximize the benefits and minimize the risks of this highly controversial procedure.

Immunosuppression Issues

The leading ethical concern in face transplantation is whether potentially improving a patient's quality of life justifies the potential long-term risks involved with immunosuppression (4–8). Patients on life-long immunosuppressive regimens suffer from significant side-effects that include an

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increased incidence of cancer, infections, and nephrotoxicity (5, 9). The increased incidence of cancers is presumably due to impaired immune tumor surveillance and increased susceptibility to viral infections stimulating neoplasm formation. In a retrospective study on renal transplant recipients almost half of the patients developed cancer, half of these malignancies becoming clinically evident within the first 5 years of transplantation, increasing to 71% at 10-year follow-up (10). Skin cancer was by far the commonest, accounting for 20% of these cancers (10). The incidence of squamous cell cancer is reported to be 65 to 250 times higher and that of basal carcinoma 10 times higher in renal transplant recipients when compared with the general population (11). Many of these tumors occur in the facial area and their tendency to metastasize is higher than in general population (12). Other frequently seen cancers are lymphoproliferative disorders, cancers of the pharynx, larynx and oral cavity, and Kaposi sarcoma (10). However, there is evidence to suggest that the above estimates may not completely apply to face transplant recipients, as the studies on which these estimates are based, used different immunosuppressive drugs other than those that will be and are being used in facial transplantation (13). Recent renal transplant experiences with tacrolimus, mycophenolate mofetil and steroids combination, which is the current immunosuppressive regimen in composite tissue allotransplantation, revealed that the cumulative incidence of cancer is lower at the relatively early time point of 3-year follow-up. To date, none of the hand transplant recipients developed evidence of cancer (13).

Immunosuppression also leads to opportunistic infections including *Pneumocystis carinii* pneumonia, viral disease (e.g., cytomegalovirus), and fungal infections (14). The biggest risk is in the early posttransplant period due to immunosuppression loading. The key to treatment is a high index of suspicion, liberal use of laboratory tests, and early, focused treatment. There is also an increased risk of hypertension, diabetes, nephrotoxicity, GI adverse effects, and posttransplant bone disease as secondary side effects of immunosuppressive medications.

From an immunological perspective, a facial allograft is expected to behave more like a hand allograft than solid organ transplantation. Based on extrapolations from hand transplants data (15), the incidence of acute rejection in face transplantation is estimated to be between 10% and 70% (13). Risk of graft loss, however, is expected to be minimal, due to early recognition by visual inspection and successful reversal of rejection with high-dose systemic steroids and topical drugs (tacrolimus or steroids, or both) (15). The rate of chronic rejection of a face allograft is harder to predict and cannot be quantified due to lack of long-term follow-up results with composite tissue allotransplantation.

Patient Selection

Selection Criteria

Careful patient selection is critical to the final success of facial transplantation. Failure to comply with the immunosuppressive regimen of medications can have catastrophic results leading to rejection of the facial part. Poor selection of patients could negatively affect the future of this reconstructive procedure and fuel ethical and legal disputes. Having the

TABLE 1. Patient selection criteria

Inclusion criteria	Exclusion criteria
1. Patient must be a previous organ recipient currently on immunosuppressive medications and	1. Patients previously noncompliant with care and follow-up
2. (A) Severe facial disfigurement, defined as loss of at least 25% of the facial surface, or loss of important facial units (i.e., nose, upper, or lower lip) ^a or (B) Patients diagnosed with cancer necessitating resection that would likely result in severe facial disfigurement ^a	2. Patients with history of psychiatric illness on medications 3. Patients who received liver, lung, or heart transplantation

^a Outcome of an alternative reconstructive method should be considered unfavorable or unsatisfactory.

risk and benefit balance in mind, we developed our "Patient Selection Criteria" (Table 1) to maximize the benefits and minimize the risks associated with face transplantation.

We currently share the concern that the life-long immunosuppression associated with facial transplantation may not outweigh its benefits as compared with the alternative reconstructive methods. At the same time, extensive soft tissue defects in the face are difficult or impossible to reconstruct and conventional reconstructive methods (16–19) are associated with poor esthetic and functional outcomes and often subject the patients to numerous revision surgeries with suboptimal results. To address this highly controversial issue, we asked ourselves the question of which patient population would risk less and overall benefit more from undergoing face transplantation, and identified those who are currently on immunosuppressive therapy the most suitable candidates. These patients are at increased risk of malignancy, particularly skin cancer commonly located in the facial region, necessitating surgical resection and some form of facial reconstruction. They also have to take life-long immunosuppressants to prevent rejection of their primary transplanted organ or tissue that will minimize the need for additional immune suppression associated with the facial allograft (see below).

Moreover, being a previous organ recipient diminishes the difficulty of complying with the strict postoperative immunosuppressive regimen, commonly encountered by organ transplant recipients. These patients understand the complicated issues related to side effects and risks associated with immunosuppression. Some degree of noncompliance to immunosuppressive regimen is common in transplanted patients (20). Excluding patients with history of noncompliance or patients with history of psychiatric illness will be a great advantage as noncompliance leads to graft loss, and was probably the cause of graft rejection in the first hand transplant (15).

One of the functions of skin is to provide a barrier between the "outside" world and the body. As such the skin has a number of defenses including potent professional antigen presenting cells, whose function is to present foreign antigens

to the body's immune system. Therefore, a face transplant that includes skin would elicit a stronger alloimmune response than other solid organ transplants and it is possible that these professional antigen presenting cells trigger an immune response to other transplanted organs. Sequential transplant of islet cells after kidney transplantation has lead to at least one case of acute rejection of a kidney allograft, although whether this was caused by the islet cell transplant or other factors, including modification of the immunosuppressive regimen is difficult to say (21). On the other hand, there is ample evidence from animal studies that when skin is transplanted after heart or kidney transplantations, the skin transplantation can be rapidly rejected without affecting the primary transplant (22).

In addition, there are numerous studies that describe favorable outcome of a second sequential organ transplantation (e.g., kidney after a heart transplant), coming from different donors at a different time and therefore presenting a similar difference in antigenic stimulation as the tissue in our study. For this reason, we exclude previous recipients of vital organs (heart, lung, liver) from our study. Ultimately, if there are signs of primary organ rejection the transplanted facial unit can be removed and standard reconstruction performed. This should immediately stop the process of primary organ rejection, as the stimulating tissues are no longer present.

Selection Process

Because of unique surgical, medical, emotional, social, behavioral, and medicolegal consequences resulting from the operation, a multidisciplinary effort must be used to ensure that the patient selected is prepared for not only the operation and postoperative care and maintenance, but also the expected publicity and media attention (5). This multidisciplinary approach should start early in the stage of protocol development and continue for the whole period of patient selection, surgical procedure, postoperative care, and follow-up.

The focus of our study is on previous organ recipients currently taking immunosuppressants who require face transplantation. Candidates would be postfacial trauma or burn patients with severe facial disfigurement, or patients diagnosed with facial skin cancer necessitating resection that would likely result in severe facial disfigurement. Given that our patients have been on immunosuppression for some time, we anticipate the majority of our prospective candidates to be facial cancer patients. Victims of facial trauma or burns are likely to be the other candidates. These patients will be identified in conjunction with transplant surgical team, transplant medical team, and ENT services. Outreach starts with local institutions, followed by regional and national search. The option of facial transplantation will be offered to these patients in their regular follow-up. Subsequently, the candidates will be referred to plastic surgery clinic for screening. Initial assessment includes history and physical examination, and an in-depth explanation of the preoperative preparation and donor selection process, the transplant itself, the postoperative hospital stay, and the follow-up outpatient regimen. The risks, the benefits, and alternative treatments will be discussed. Suitable candidates will then be assessed by a social worker, who will perform screening focusing on history of alcohol or drug abuse, eval-

uation of emotional problems and stress management, medical compliance, and other relevant factors. Subsequently, candidates and their support network will be referred to a psychiatric team that specializes in treating patients with facial deformities, to assess their understanding of the facial transplant process, their knowledge of the possible alternative treatments, their ability to deal with the possible identity change and the possible media exposure, their expectations, and their home social support system. An outside psychiatrist (study independent) will also see the candidates for second opinion. If the subject is considered qualified, a meeting will take place specifically to sign the consent form. The person will then be added to the transplant waitlist and the regional Organ Bank notified.

Technical and Surgical Aspects

Our protocol focuses on partial face transplantation in patients with severe facial disfigurement. We define severe facial disfigurement as loss of at least 25% of the facial surface or loss of important facial units or subunits, including nose, upper and lower lips with a variable degree of chin and cheek (Fig. 1). Tissues in the central part of the face are highly specialized and anatomically distinct. The loss of both upper and lower lips or nose is functionally and esthetically difficult or impossible to repair because of lack of similar tissues that could be used for reconstruction. In comparison with total face transplantation, facial flap procurement is less challenging in partial face transplantation because of shorter ischemia time and reduced risk of vascular failure of the facial flap. In addition, in case of the vascular failure of the flap in the immediate postoperative period, the "rescue procedure" using conventional reconstructive methods would be easier to per-



FIGURE 1. Central and lower face transplant.

form (23, 24). Furthermore, partial face transplantation may be associated with less dramatic change of recipient's facial appearance, and less chance of donor identification; therefore, minimizing (at least in part) some of the ethical concerns regarding the identity aspects and the resulting psychological consequences of face transplantation for both the donor and recipient's side. We agree with ASRM/ASPS position paper (3) that the outcomes of alternative reconstructive options should be considered unfavorable or unsatisfactory before proceeding with face transplantation.

No patient will be given the choice of facial transplantation as the primary reconstructive option, as the timing of donor/recipient match is unpredictable and a delay in the treatment of cancer, trauma or burn of the face unacceptable. In the case of facial trauma or burn, the patient will be acutely taken care of using standard surgical techniques, and the option of face transplantation would be presented once the patient recovered and is able to make his or her own decisions. Likewise, cancer patients will first be treated according to standard protocols to avoid any delay in starting the treatment and therefore adversely affecting the prognosis. Thus, most patients who will be participating in the study will have undergone a standard reconstructive procedure.

Donor Selection

Facial transplantation is unique in a sense that in addition to tissue antigen match, consideration should also be given to other variables such as skin color, texture, age, and gender (6). Moreover, recovery of the facial flap will create a sizeable defect that may not be acceptable to the donor and his or her family. This will significantly limit the donor's availability and prolongs the donor selection process. To facilitate the matching process, some degree of mismatch in complexion or age may therefore be allowed, which can be camouflaged with makeup. Because of individual variability it is difficult to develop set criteria for selecting the donors, however, a donor may be considered suitable once the skin color and gender is matched within the range of 20 years of the recipient. It is important to notify the recipients that skin color and texture will not be perfect and they should be ready for a mismatch to some degree.

During developing the face transplantation protocol a close collaboration between the surgical team and the regional Organ Bank is crucial in training the "Donor Recovery Team," helping to develop special donor consent forms, teaching the protocol to the bank staff, and developing a media plan to cover local, national, and international press attention, while maintaining the donor and recipient's confidentiality.

Surgical Procedure

Three surgical teams will be working simultaneously on the donor and recipient. Two teams will be performing donor surgical procedures, working on the radial forearm flap and the facial flap. The radial forearm flap will be implanted on the recipient's chest using microsurgical techniques, to avoid frequent biopsies of the facial flap in the postoperative period. This graft is specifically chosen as it anatomically resembles the facial tissues in its structures. A special template matching the dimensions and shape of the recipient's facial defect or injury will be made on enrollment that will assist in raising the

facial flap. The third team will be preparing the recipient's facial bed, timed with the recovery procedure to minimize delays and warm or cold ischemia of the transplanted part. Most probably the two operations will have to be performed at separate hospitals. The risk of acute flap failure as a result of vascular problems can be minimized by reducing ischemia time and applying meticulous microsurgical techniques. Only heart beating donors will therefore be considered to maximize the chances of timely transplantation and reduce the risk of ischemic injury to the transplanted graft. The ischemic time of the facial flap should be kept at a minimum, ideally less than 4 hr. The possibility of the free tissue transfer failure, reportedly 2% to 4% in experienced centers, should be considered and "rescue procedures" using conventional reconstructive methods should be outlined. A prosthetic material to fit in the donor's facial defect will be made in advance of the surgery to cover the donor's facial defect once recovery of the facial graft is complete. This will make it easier for all those who must work with the body after recovery, for example, OR staff, funeral directors, etc., and also more acceptable for the donor's family.

Informed Consent

Another complex issue surrounding facial transplantation is the extent of developing an informed consent. A thorough multifaceted consent form covering surgical, medical, and psychological aspects of the procedure must be developed and given to the prospective candidates, their family, and the donor family as well (5). Total face transplantation compared with previously performed central and lower face (2), also referred to as partial face transplantation, is associated with more complex technical, ethical, and psychological issues, and is not considered in our protocol. It must be emphasized that face transplantation is still considered an experimental procedure, and while every new step is based on the best available evidence and standard of care, informed consent is almost impossible to obtain because of the overwhelming lack of objective clinical information. The patient cannot be adequately informed about consequences of the operation that are unknown to the surgeon himself. Likewise, patients must be aware of the alternative surgical procedures for treating facial deformities, and the reasons for considering the facial allograft transplantation as a potential superior reconstructive option. The major risks that the patient must comprehend before undergoing the transplantation include risk of graft loss due to surgical failure or acute transplant rejection, unknown risk of chronic rejection and functional failure, risks associated with life-long immunosuppression, and unknown risk of previous transplant rejection (see above). In the case of postcancer reconstruction, there is also a possible risk of primary cancer recurrence due to immunosuppression loading in the immediate postoperative period, which emphasizes the importance of ensuring cancer remission before performing the face transplantation.

Immunosuppressive Protocol

Given that our patients are previous organ recipients, they will already be taking immunosuppressive medications. Modern immunosuppressive maintenance regimens routinely use combination immunosuppression as the standard, to suppress multiple immune system pathways and reduce

drug toxicity on the assumption that most chronic drug toxicities are to some extent dose dependent (9). Most common maintenance regimens consist of a calcineurin inhibitor, either cyclosporine A or tacrolimus, an antiproliferative agent, mycophenolate acid, azathioprine, or sirolimus, and corticosteroids. Currently, the most commonly used maintenance immunosuppression in kidney transplant recipients in the United States is the tacrolimus, mycophenolate acid and steroid combination (25), which has also been successfully used in recent experimental hand and face transplantation and is likely to remain the main regimen in our study. Therefore, we anticipate that our patients continue with their current maintenance immunosuppressive drugs with certain caveats. A minimum of 1-year wait after the first transplant is required, as the risk of acute rejection will be much lower then. Because of increased alloimmune response, patients will get induction therapy with an IL-2R antibody, in addition to their maintenance immunosuppressive regimen. It is possible that the patients who are candidates for a facial transplant because of cancer will be on minimal immunosuppression based on sirolimus, as this has been shown to have anti-cancer effect. In the early posttransplant period, it will be important to avoid the use of sirolimus as this drug interferes with wound healing (26). It will also be important to assess the individual risk of future skin cancer in deciding the exact immunosuppressive regimen for patients.

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