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REVIEW ARTICLE

Facial transplantation: historical developments and future directions

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Abstract

Objective: To present the clinical outcomes obtained by the first facial transplant teams worldwide, reviewing current practice and addressing controversies.

Methods: A bibliographic search of Medline and Embase databases was performed, and a comparative analysis of all articles published from 1980 to the present was conducted. Two independent investigators screened the manuscripts in accordance with pre-defined criteria.

Results: A total of 12 partial and 5 full facial transplants were recorded in the literature. Procedures included partial and near-total facial myocutaneous flaps, and complex osteomyocutaneous grafts. Fifteen patients had fully vascularised grafts, and two patients died of transplant-related and infectious complications.

Conclusion: Facial transplantation can restore quality of life and enable the social re-integration of recipients. Results published by the first facial transplant teams are promising. However, long-term reports of aesthetic and functional outcomes are needed to more precisely define outcomes. In addition, significant technical, medical and ethical issues remain to be solved.

Key words: Facial Transplantation; Composite Tissue Allografts

Introduction

Vascularised facial allotransplantation is a viable option for the repair of complex craniofacial defects not amenable to autologous reconstruction with conventional reconstructive techniques. Since 2005, facial transplantation programmes have been successfully established in France, the USA, China and Spain, with a total of 12 partial and 5 full procedures reported in the literature.[1–10] Indications for the procedures included traumatic injury, neurofibromatosis and disfigurement following resection of extensive tumours. Traumatic injuries were caused by animal attacks, gunshots, burns and falls. Several episodes of acute graft rejection occurred and were successfully managed with intensification of immunosuppression. Two recipients died at 2 months and at 27 months post-transplantation respectively: the first death in China was concluded to be due to septic multi-organ failure following voluntary cessation of immunotherapy.[2] In France, a patient with a concomitant facial and bilateral below-the-elbow (upper limb) composite tissue allograft suffered a cardiac arrest triggered by an obstructed tracheotomy tube.[6] All remaining grafts were viable and have yielded satisfactory functional and aesthetic outcomes, with near-complete restoration of sensation. Table I summarises the main characteristics of facial transplantations performed from 2005 to 2012.[1–10]

In this report, we delineate the historical developments and future directions of facial transplantation, based on the current literature and experience of teams across the world. We wish to inform physicians of the surgical and immunological models that have been adopted, and to raise awareness of the ethics of facial transplantation, outlining the challenges of establishing a facial transplantation programme.

Materials and methods

The literature search was carried out using two electronic databases, Medline and Embase. A search of articles published from 1980 to the present with titles that included the terms 'facial', 'face', 'transplant' and 'transplantation' was conducted. Additional articles were obtained from the reference lists of identified publications.

Two independent reviewers screened 594 manuscripts. Articles with repetition or duplication of original data, animal studies, and non-English language papers were excluded. A total of 58 manuscripts were selected for the review.

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TABLE I
SUMMARY OF FACIAL TRANSPLANTATION CASES RECORDED IN THE LITERATURE

Facial transplantation team (year conducted); country	Recipient age (y), sex	Indication	Defect
Devauchelle *et al*. (2005);[1] France	38, F	Animal attack	Nose & lip
Guo *et al*. (2006);[2] China	30, M	Animal attack	Mid face
Lantieri *et al*. (2007);[3] France	29, M	Bilateral plexiform neurofibromas	2/3 lower face
Siemionow *et al*. (2008);[4] USA	45, F	Gunshot injury	Mid face
Cavadas *et al*. (2009);[5] Spain	42, M	Cancer	1/3 lower face
Lantieri *et al*. (2009);[6] France	27, M	Gunshot injury	2/3 lower face
Lantieri *et al*. (2009);[6] France	37, M	Burn	2/3 upper face
Lantieri *et al*. (2009);[6] France	33, M	Gunshot injury	2/3 lower face
Pohamac *et al*. (2009);[7] USA	29, M	Burn	2/3 lower face
Barret *et al*. (2010);[8] Spain	31, M	Gunshot injury	Full face
Gomez-Cia *et al*. (2010);[9] Spain	35, M	Bilateral plexiform neurofibromas	2/3 lower face
Lantieri *et al*. (2010);[6] France	35, M	Bilateral plexiform neurofibromas	Full face
Lantieri *et al*. (2011);[6] France	45, M	Gunshot injury	2/3 lower face
Lantieri *et al*. (2011);[6] France	41, M	Gunshot injury	2/3 lower face
Pohamac *et al*. (2011);[10] USA	35, M	Burn	Full face
Pohamac *et al*. (2011);[10] USA	30, M	Burn	Full face
Pohamac *et al*. (2011);[10] USA	55, F	Animal attack	Full face

Y = years; F = female; M = male

Surgical outcomes

Progress in reconstructive microsurgical techniques and immunotherapy have advanced the field of composite tissue allotransplantation, which has been performed on facial and abdominal wall structures, the larynx, the tongue, and the knee.[11] Facial composite tissue transplantation incorporates surgical techniques used in general transplantation and reconstructive surgery. The surgical act of transplantation can be broken down into graft harvesting, graft preservation, and transplant grafting with nerve and vessel anastomosis. The procedure requires meticulous tissue handling, microanastomotic skills, and appropriate graft harvesting and preserving methods.

The graft harvesting method varies according to individual surgical units, and on the amount and depth of tissue required to achieve optimal aesthetic and functional outcomes. Harvesting can commence by raising a bicoronal flap in a caudal direction to the preauricular region. Dissection is continued in a subgaleal plane towards the supraorbital region. The supraorbital and supratrochlear nerves are identified as they exit from their foramina; the bone surrounding the nerves can be trimmed using an osteotome or drill, to increase the length of nerve harvested.

If eyelids are required, dissection can proceed along the palpebral conjunctival reflection, with transection of the levator muscles, incision through the conjunctiva and dissection of the canthal ligaments at their bony insertions. This will allow detachment of the graft through the deep soft tissue layer until the inferior orbital rim is reached, allowing preservation of the upper and lower eyelids.[12] In order to harvest the nose, osteotomies can be performed to separate the nasal bone from the underlying malar eminence, allowing a full nose composite within the facial graft.[12–14]

Dissection at the preauricular incisions progresses in a lateral to medial direction on top of the parotid fascia. Facial nerve branches can be individually identified, tagged and elevated as part of the allograft.[12] Alternatively, the parotid gland, with the facial nerve dissected at its main trunk as it exits the stylomastoid foramen, can be harvested as part of the allograft.[14] Depending on the material required, either muscle alone can be harvested by continuing dissection in the subperiosteal plane, or osteotomies can be performed in order to release the zygoma and maxilla as required.[11–14]

The graft is released up to the level of the pyriform aperture of the nose via a superior to inferior dissection, and to the level of the modiolus at the angle of the mouth via a lateral to medial dissection. Perioral tissues are then raised in a subperiosteal plane, along the gingivobuccal sulcus and inferiorly to the mandibular border, allowing for sufficient amounts of tissue harvesting for intraoral inset in the recipient.[10–14]

Before releasing the lower portion of the grafts, the facial artery and vein are identified and protected. The facial artery can be identified via dissection from the carotid arteries distally. Once the facial vessels are identified and protected, the dissection can continue up to the mentum, with preservation of the mental nerve. At this point, complete dissection of the lower face will have been achieved, and the bilateral preauricular incisions can be extended inferiorly to allow neck dissections so that the sternocleidomastoid muscle, and the internal and external jugular and retromandibular veins, can be ligated and divided as required.[8–15]

Once the graft has been obtained, maintaining the viability is crucial. The actual ischaemia time of facial grafts is not known; however, based on known muscle ischaemia times, authors recommend reperfusion of the graft within 4 hours of onset of cold ischaemia.[12] Alternatively, a temporary vascular anastomosis on the recipient's femoral vessels will allow reperfusion while the rest of the surgical procedures are performed.[14]

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Facial nerve and vessel harvesting, and eventual anastomoses, will vary depending on the recipient's needs, and on the quality of both the donor's and recipient's vessels. Vessel quality will usually be determined by computed tomography angiography and magnetic resonance imaging. Most vascular anastomoses are performed in large diameter vessels, such as external carotids and jugular veins, in order to minimise thrombosis.[12–14] However, complete facial revascularisation can also be achieved by means of a single pedicle anastomosis of the facial vessels.[8]

Facial nerve transplantation can be achieved by either anastomosing the nerve at the main trunk, with or without the parotid gland, or by anastomosing individual branches peripherally by performing an intraparotid nerve dissection.[9,12] Smaller calibre nerves, such as the supraorbital, infraorbital and mental nerves, can also be anastomosed.[12] The remainder of the graft containing muscle and skin can be anastomosed to underlying recipient structures in a medial to lateral, and inferior to superior, direction. Bony integration will require appropriate osteotomies and plating.

Complications are common to all surgical procedures. With respect to facial transplantation, blood loss can be particularly high.[1–4,9] One case reported the need to transfuse 24 units.[9] In addition, in light of the prolonged surgical time, and associated immobilisation and blood loss, rhabdomyolysis is a reported complication.[9]

Immunological outcomes

Despite familiarity with the immunobiology of facial transplantation, some of its fundamental characteristics remain poorly recognised. Current practice is guided by previous experience with hand composite tissue allografts and solid organ transplants. The risks of immune rejection are not established; however, a working party report from the Royal College of Surgeons of England estimates that facial composite tissue allografts carry a 10 per cent risk of acute rejection and graft failure in the first year, and a 30–50 per cent risk of chronic rejection in the second to fifth year.[16] In solid organ transplants, the risk of graft failure is proportional to the type and amount of tissue grafted, and to prior recipient sensitisation to donor major histocompatibility complex antigen.

The importance of donor–recipient immune disparity in facial transplantation is not clear, despite available documentation on the detrimental effect of human leukocyte antigen mismatch in solid organ transplants.[4,17–19] Numerous episodes of acute rejection have occurred, none correlating with human leukocyte antigen mismatch. Chronic rejection has not been reported, despite being a principal cause of morbidity and mortality in renal and cardiothoracic transplants.[20] Regular graft biopsies and immunohistological analyses are examined for vessel obstruction with vasculopathy and neointimal hyperplasia when monitoring for chronic graft rejection in facial transplantation.[21] Surgical removal and re-transplantation of the allograft may be necessary if severe rejection refractory to pharmacological therapy occurs, and this may carry a high psychological burden.

Treatment protocols utilised have universally included an anti-thymocyte globulin for induction, and tacrolimus, mycophenolate mofetil and prednisolone for maintenance.[22,23] With good compliance, this regimen has been effective at preventing graft loss. However, dose-dependent toxicity, opportunistic infections, and solid organ and cutaneous malignancies have occurred.

Donor bone marrow infusions, anti-interleukin-2 receptor antibodies and X-ray irradiation have been experimentally trialled; these demonstrated no significant reduction of side effects.[18,24] Tacrolimus has been shown to cause hypertension and nephrotoxicity characterised by interstitial fibrosis and tubular atrophy. Long-term glucocorticoids are associated with diabetes, secondary adrenal insufficiency, hypertension and osteopenia. Infections with cytomegalovirus, Epstein–Barr virus, herpes simplex virus, *Pneumocystis jirovecii* and opportunistic fungi have increased the risk of post-operative life-threatening sepsis.[25] Squamous cell cancers, cancers of the lung and colon, and cancers of viral aetiology (non-Hodgkin lymphomas, Kaposi's sarcoma and cervical cancer) have also been recorded, while lymphoproliferative disorders have not occurred.[22,23]

There is promise that tolerance may develop after five or more years of use of the triple-therapy agents.[26] Current research is developing alternative induction protocols and immunosuppressive agents with better safety profiles. The clinical application of new drugs is limited, however, and further studies are warranted.

Ethics of facial transplantation

The face enables breathing, eating, communicating and social interacting. Furthermore, it provides information about identity, age, gender and ethnicity. Patients with severe craniofacial deformities suffer functional and aesthetic abnormalities, which are often accompanied by a sense of loss of identity. This is aggravated by the notion that a person without a face is considered 'less human' in some contexts.[27] Positive and negative behavioural responses to rewarding and aversive faces respectively have been demonstrated by parametric analysis of the reward circuit in the human brain, and appear to be dopamine-mediated. This suggests that behavioural responses to 'monstrous' faces, such as avoidance, are subconscious in nature.[28]

Autologous tissue transfer and reconstructive surgery have a limited application in the repair of multiple facial subunits. Facial transplantation can improve quality of life and restore social functioning in severely deformed patients. Facial transplantation is currently experimental as precise long-term outcomes are unknown, and significant morbidity and mortality may occur. The Declaration of Helsinki guidelines can aid an ethical and professional decision concerning

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experimental procedures on human subjects: 'Where an intervention does not exist or has not proved effective, the physician may offer interventions with unknown outcome to patients if it can restore health or alleviate suffering, and this should be made as research in order to evaluate its efficacy'.[29]

The ethical and technical boundaries governing the facial transplantation debate mainly centre on the risk of life-long immunosuppression and the issue of informed consent. The notion that the procedure may be performed for aesthetic reasons or in poorly equipped centres, and the potential burden of graft failure, are also matters of concern.[26,30–35] It is debated whether life-threatening risks are ethically justifiable in light of a non-life-threatening condition. In response to this, some argue that medicine often delivers care associated with risks, which are justified when outweighed by the benefits. Renal transplants are similarly undertaken on candidates who are otherwise able to remain on haemodialysis, and as facial transplant patients are younger and healthier, the risks are lower in these patients; benefit analysis findings are in favour of transplantation.[36,37]

The respect for human dignity is a pillar of contemporary research bioethics. Patients have a right to autonomy and to give informed consent. Competence, disclosure, medical literacy, understanding and voluntariness guide an informed decision-making process. In facial transplantation, this process is complicated by unknown long-term results.[38] In order to best understand the known risks, alternative therapies and outcomes of conventional reconstructive procedures, facial transplant patients should become an active part of the team.[39] A bioethicist working closely with the patient and their family, exploring the motives for undergoing the procedure and the perception of benefits, should guide a patient-centred decision-making process.[40] It is especially important that the consequences of life-long immunosuppression are explained. The patient should be aware that if chronic rejection ensues, there may be a functional and aesthetic regression from the pre-transplantation state. If these facts are fully comprehended, informed consent can be considered valid. Low socio-economic status, poor pre-operative mental and physical health, and frailty are contraindications to facial transplantation as they are associated with poor medical literacy and cognition, or low post-operative outcomes in solid organ transplant recipients.[41]

Physicians should disclose information as transparently as possible, and list all risks, including minor and major side effects and fatalities. The detail of disclosure should be guided by the patient's desire to learn about their illness, as both under-informing and over-informing has been linked to heightened anxiety levels and poor outcomes.[42]

Establishing a facial transplantation programme

Implementing a facial transplantation programme is a complex process that presents significant logistical challenges. The American Society for Reconstructive Microsurgery and the American Society of Plastic Surgeons recommend that facial transplantation is performed on victims of severe facial disfigurement (defined as more than 25 per cent of total facial structures and including central facial units) after conventional autologous reconstruction techniques have yielded sub-optimal results.[7] Indications are in continuous evolution, although it is generally accepted that the aim of facial transplantation is to restore functional deficits.[43]

Siemionow and colleagues, who pioneered facial transplantation in the USA, advise that the procedure be undertaken at a university-based hospital, with a designated multidisciplinary team available around the clock.[44] The team should work closely with staff at an active basic science laboratory and publish their findings transparently in order to advance the international field. Experienced craniofacial microsurgeons, maxillofacial surgeons, transplant surgeons, immunologists, infectious disease specialists, psychologists and intensivists should be recruited, together with social workers, a patient advocate, ethicists, physical and speech rehabilitation staff, institutional media, liaison and public relations personnel, and security.[44] The team leader requires prior experience with transplantation, as he or she co-ordinates and oversees all aspects of the programme, and is responsible for presenting the benefit-to-risk analysis and informed consent protocols to the independent review board.[7] Various government agencies specific to the country where the programme is undertaken are involved. In the USA, the local organ procurement organisation evaluates and procures facial allografts, and ethical regulatory bodies approve and oversee the protocol.[45]

Funding can dictate the feasibility of facial transplantation. In the USA, funding has been granted by institutions, awards, and private or public endowments, including military forces aiming to help soldiers with burns and blast injuries.[44] Alternative sources of funding are required if facial transplantation is to become part of routine care. The lifetime costs of one case of facial transplantation is estimated to be between $250 000 and $1500 500 per patient, which far exceeds the proposed threshold of $50 000 per quality-adjusted life year and limits the possibility of comprehensive government funding.[46,47] Ultimately, the availability of resources that cover the cost of facial transplantation will depend on how well society perceives the procedure and how recipients re-integrate in society. Reassuringly, the first facial transplant recipient, now eight years post-operative, has demonstrated significant functional and aesthetic restoration, and 2 of the 17 recipients have returned to employment. Media coverage has enhanced awareness of facial transplantation amongst the public and the medical community, and has contributed to the increased acceptance of the procedure.

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Conclusion

The controversies governing facial transplantation centre on surgical and immunological risks, and the ability to provide informed consent. Although long-term outcomes are not yet fully available, reports indicate that significant cosmetic and functional benefits, and successful social re-integration of recipients, are achieved by facial transplantation. The next challenge is to prevent immune-pathogenic responses, while diminishing the burden of life-long immunosuppression. Further understanding of the complex immune response will provide insight into effective treatment strategies and improve donor-specific tolerance. Experimental studies are ongoing; these are leading to a successful clinical translation in autoimmune disease and solid organ transplants. If novel therapeutic strategies are extended to composite tissue allografts, the field of facial transplantation may dramatically expand in both adult and paediatric surgery.

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