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Review

Clinical outcomes of facial transplantation: A review

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ABSTRACT

A total of 18 composite tissue allotransplants of the face have currently been reported. Prior to the start of the face transplant programme, there had been intense debate over the risks and benefits of performing this experimental surgery. This review examines the surgical, functional and aesthetic, immunological and psychological outcomes of facial transplantation thus far, based on the predicted risks outlined in early publications from teams around the world.

The initial experience has demonstrated that facial transplantation is surgically feasible. Functional and aesthetic outcomes have been very encouraging with good motor and sensory recovery and improvements to important facial functions observed. Episodes of acute rejection have been common, as predicted, but easily controlled with increases in systemic immunosuppression. Psychological improvements have been remarkable and have resulted in the reintegration of patients into the outside world, social networks and even the workplace. Complications of immunosuppression and patient mortality have been observed in the initial series. These have highlighted rigorous patient selection as the key predictor of success.

The overall early outcomes of the face transplant programme have been generally more positive than many predicted. This initial success is testament to the robust approach of teams. Dissemination of outcomes and ongoing refinement of the process may allow facial transplantation to eventually become a first-line reconstructive option for those with extensive facial disfigurements.

1. Introduction

The world's first allotransplant of a human face was successfully performed in Amiens, France in November 2005.[1] This signalled the emergence of a new reconstructive option for those with extensive facial disfigurements. Composite tissue allotransplantation of the face is currently in its experimental phase, with a total of 18 procedures reported to date (Table 1). Following the early positive experience observed in hand transplantation and encouraging experimental evidence there was optimism that facial transplantation could be successfully performed by the late 1990s. Subsequently the technical, immunological, ethical, psychological and legal aspects of the procedure were heavily debated. The Royal College of Surgeons of England produced working party reports in 2003[2] and 2006[3] and teams throughout the world made contributions to the medical literature, addressing the risks and benefits of facial transplantation.[4–12] This paper uses the challenges highlighted in these early papers to examine the surgical, functional and aesthetic, immunological and psychological outcomes of the face transplant programme so far.

2. Surgical outcomes

Prior to the first case in Amiens, there were varied opinions on the surgical challenge of facial transplantation, with some teams suggesting that the procedure would be no more difficult than conventional reconstructive techniques[10] and others raising significant concerns.[4] However, surgical feasibility of facial transplantation was predicted, based on the success of microsurgical techniques.[2,3,8] Failure of vascular anastomoses was identified as a potential risk that could result in removal of the transplanted tissue, rendering the recipient at the bottom of the reconstructive ladder.[2–5] Thus far, facial allografts have varied in extents of skin, muscle and bone harvested (Table 1), but all have been grafted successfully and remained viable following surgery. Post-operative venous thrombosis has been reported by the Barcelona team, requiring reanastomosis on post-operative day three.[13] There have been no further concerns over the vascular anastomosis in this patient.

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Table 1
Overview of face transplants performed to date.

Team (Surgeon)	Date	Location	Recipient (age/gender)	Mechanism of injury	Donor	Allograft	Current Status
Devauchelle/ Dubernard (1)	Nov 2005	Amiens, France	38, F	Dog bite	Brain dead, heart-beating	Peri-oral muscles, oral and nasal mucosa, nose, bilateral facial vessels, zygomatic, buccal and mandibular facial nerve branches, infra-orbital and mental nerves	Alive
Guo	Apr 2006	Xi'an, China	30, M	Bear attack	Non heart-beating	Parotid gland, partial buccal mucosa, partial masseter, partial zygomatic arch, lateral and infra-orbital walls, maxillary sinus, upper lip, nose, nasal bone	Died at 27 mo
Lantieri (1)	Jan 2007	Paris, France	29, M	Plexiform neurofibroma	Brain dead, heart-beating	Bilateral parotids, nose, oral mucosa, facial, mental and infra-orbital nerves, bilateral external carotid arteries, thyrolinguofacial veins	Alive
Siemionow	Dec 2008	Cleveland, USA	45, F	Shotgun injury	Brain dead, heart-beating	Total nose, lower eyelids, upper lip, total infra-orbital floor, bilateral zygomas, anterior maxilla with alveolus, anterior hard palate, bilateral parotids, bilateral facial arteries, external jugular veins, left posterior facial vein bilateral facial nerves	Alive
Lantieri (2)	Mar 2009	Paris, France	27, M	Shotgun injury	Brain dead, heart-beating	Parotid glands, masseter, oral mucosa, upper and lower lips, chin, nose, premaxilla, bilateral anterior maxillary sinus wall, external carotid artery, external jugular vein, thyrolinguofacial trunk, facial nerve, supra- and infra-orbital nerves	Alive
Lantieri (3)	Apr 2009	Paris, France	37, M	Burns	Brain dead, heart-beating	Scalp, ears, bilateral parotids, masseter, oral mucosa, upper and lower lips, external carotid artery, external jugular vein, thyrolinguofacial trunk, facial nerve, mental and infra-orbital nerves	Died at 2 mo
Pomahac (1)	Apr 2009	Boston, USA	59, M	Electrical injury	Brain dead, heart-beating	Facial mimetic muscles, upper lip, nose, maxilla and hard palate, oral mucosa, bilateral facial arteries, left facial vein, right external jugular vein, facial nerve, infra-orbital nerve	Alive
Cavadas	Aug 2009	Valencia, Spain	42, M	Radiotherapy damage	Brain dead, non-heart beating	Skin from oral commissures to earlobes and down to upper neck, mandible from right angle to left condyle, tongue, floor of mouth, hyoid bone, suprahyid muscles, six salivary glands, right lingual and facial arteries, left internal maxillary, lingual and facial arteries, bilateral common and internal carotid arteries, bilateral external jugular, thyrolingual and internal jugular veins.	Alive
Lantieri (4)	Aug 2009	Paris, France	33, M	Shotgun injury	Brain dead heart-beating	Lower two thirds of nose, mouth, maxilla, jaw skin and oral mucosa	Alive
Devauchelle/ Dubernard (2)	Nov 2009	Amiens. France	27, M	Pyrotechnic explosion	Brain dead, heart-beating	Maxilla, mandible lower lip, floor of mouth and chin	Alive
Gomez Cia	Jan 2010	Seville, Spain	35, M	Neurofibromatosis	Non-heart beating	Lips, oral mucosa, perioral muscles, bilateral cheeks, bilateral parotid glands, bilateral facial nerves, bilateral mental nerves, bilateral infra-orbital nerves, bilateral common carotid arteries, bilateral jugular veins, osseous chin segment	Alive
Barret	Mar 2010	Barcelona, Spain	31, M	Shotgun injury	Brain dead heart-beating	Facial skin and muscles, eyelids, lacrimal ducts, hard palate, floor of mouth, upper and lower lips, cheek mucosa, mandible, maxilla, two thirds of zygoma, nose, external carotid arteries, external jugular veins, supraorbital, infra-orbital, mandibular nerves and frontal, buccal and zygomatic branches of facial nerve	Alive
Lantieri (5)	Jun 2010	Paris, France	35, M	Neurofibromatosis	Not reported	Not yet reported	Alive

(*continued on next page*)

Table 1 (*continued*)

Team (Surgeon)	Date	Location	Recipient (age/gender)	Mechanism of injury	Donor	Allograft	Current Status
Pomahac (2)	Mar 2011	Boston, USA	25, M	Electrical injury	Not reported	Nose, lips, facial skin and muscles of facial animation	Alive
Pomahac (3)	April 2011	Boston, USA	30, M	Electrical injury	Not reported	Forehead, nose, lips, facial skin, muscles of facial animation	Alive
Lantieri (6)	April 2011	Paris, France	M	Shotgun injury	Not reported	Not reported	Alive
Lantieri (7)	April 2011	Paris, France	M	Shotgun injury	Not reported	Not reported	Alive
Pomahac (4)	May 2011	Boston, USA	57, F	Chimpanzee attack	Not reported	Forehead, nose, lips, facial skin, muscles of facial animation, left hand and partial right hand	Alive

The experimental and clinical experience of facial transplantation has allayed early concerns that allografts containing the craniofacial skeleton would not be viable if just supplied by the facial artery.[7] It was suggested that such allografts would require a branch of the maxillary artery to be raised,[14] increasing the difficulty of the retrieval process. However, Pomahac et al have shown in preclinical cadaveric dissections that numerous small arterial connections exist between the deep branches of the facial artery and the distal branches of the maxillary artery.[15] Consequently, the maxilla and hard palate of a facial allograft can receive an adequate blood supply from the facial artery alone. Subsequent to these studies, they successfully transplanted a midfacial allograft, including maxilla and zygoma based on the facial artery.[15] Furthermore, the fourth face transplant, also performed in the United States, containing maxilla and palate received its vascular perfusion from just the facial artery.[16] Despite initial fears over the revascularisation of extensive facial allografts,[4] the Barcelona group have reported patency of a flap containing the entire face on a single external carotid artery.[13] It, therefore, appears that adequate reperfusion of facial allografts can be achieved with relatively few vascular anastomoses.

Whilst all facial allografts have been successfully transplanted, some teams have described extensive intra-operative blood loss. The flap for the second procedure was procured quickly from a non-heart beating donor, with no measures taken for haemostasis, resulting in 5 L of blood loss from around the recipient wound.[17] Lantieri et al have described transfusion requirements of 10 or more units of packed red blood cells in each of their first four recipients.[18] Substantial blood loss also occurred in the second Spanish transplant, requiring transfusion of 24 units of packed red blood cells and resulting in a post-transplant dilutional coagulopathy.[19] Interestingly, this patient also developed post-transplant rhabdomyolysis, attributed to the long period of intra-operative immobilisation and extensive blood loss.[20]

3. Functional and aesthetic outcomes

Return of normal function in transplanted facial musculature and nerves were considered unlikely outcomes before the first procedure. Thus far, quick sensory recovery has been consistently described in face transplants with available follow-up reports (Table 2).[13,17,18,21–24] Lantieri et al have described thermal and mechanical sensory reinnervation occurring as quickly as three months post-surgery in the third recipient.[21] In addition, Dubernard et al reported that the entire skin surface and oral mucosa of the first allograft was sensate by the fourteenth post-operative week,[1] with complete sensory recovery to light touch, heat and cold achieved by six months.[22] Similarly, Pomahac et al have described sensory recovery, in their first patient, to light touch, heat and cold, pinprick and two point discriminaton to 15 mm by six months.[24] The third Spanish recipient, who received a facial graft containing the entire face, had regained total restoration of sensation in forehead, eyelids, cheeks and oral mucosa by four months.[13] Such complete recovery has exceeded initial expectations.[7]

The working party reports of the Royal College of Surgeons of England mentioned the use of facial slings to aid function in the event of poor motor recovery. This has not been reported so far. As predicted, restoration of motor function has been generally slower than sensory recovery (Table 2). However, Lantieri et al have demonstrated initial motor recovery as early as two months post-transplant, with complete mouth closure achieved by eight months in the fifth recipient.[21]

As foreseen in the working party reports functional outcomes of facial transplantation have been favourable.[3] Even with unsatisfactory facial nerve anastomosis in the Chinese transplant, the patient was still able to eat, drink and talk normally at two years.[17] Siemionow et al described significant functional recovery by eight months post-transplant, including restoration of smell, ability to eat solid foods, drink from a cup and speak, even in the absence of nerve coaption.[16] Importantly, there was reduction of chronic pain levels from scarred and contracted tissues, from 8/10 before the transplant to 1/10 afterwards.[23] In the follow-up report of their first four recipients, Lantieri et al have described recovery of intelligible speech in all patients between days 10 and 24 post-operatively.[18] Significant functional improvements, including oral intake and the ability to breath and smell were established almost immediately following surgery in the seventh recipient.[24] Interestingly, there have been ongoing functional improvements in the first recipient of a facial allograft at five years post-transplant. This patient is now able to chew, swallow, eat, smile, speak, drink and blow.[25]

From an aesthetic perspective, computer simulation modelling of change in appearance after facial transplantation had predicted that recipient appearance would be derived as a composite face[12] and this has been the observed clinical outcome.[26] The recipient of the first face transplant has reported that she is very satisfied with the result.[22] Siemionow et al have described their patient as reacting favourably post-transplantation, with a positive self-appearance rating of 5/10 at three weeks (her pre-transplant rating was also 5/10) and 8/10 at five months.[23] Furthermore, Pomahac et al have assessed the aesthetic outcome of their patient to be excellent at one year.[24]

Face transplant teams that have published follow-up reports thus far have described attempts to match recipients with donors of matched age, sex and skin phenotype.[1,17,18,26] Due to restrictions on face donors, Lanieri et al have described an age discrepancy in their first four transplants, performed in Paris, where donors were on average 24 years older than recipients.[18] The donor for their first case was 36 years older than the recipient. Computer simulation

Table 2
Sensory, motor, functional, aesthetic and psychological outcomes of facial transplantation.

Team	Sensory Recovery	Motor Recovery	Functional Recovery	Aesthetic Outcome	Psychological Outcome
Devauchelle/ Dubernard (1)	Light touch – 14wks Heat/cold – 6 mo	Lip occlusion - 6 mo Chin/nose muscle contractions-12 mo	Mobilise food bolus – 6 mo Symmetrical smile – 18 mo	Pt very satisfied at 18 mo	Social re-integration-12wks
Guo	Light touch – 3 mo Heat/cold – 8 mo	Poor function – levator labii superioris, levator anguli oris,	Unable to smile symmetrically – 2yrs Able to eat, drink, talk	Reported as improved Further excision of redundant tissues (7 mo, 12 mo)	Accepted new face easily
Lantieri (1)	Light touch – 3 mo Heat/cold – 3 mo	Motor recovery, seen by EMG, at 12 mo	Not reported	Reduced concern about appearance post-op	Objective improvement in quality of life and appearance. Began job at 13 mo
Siemionow	Light touch – 6 mo Heat/cold – not reported	Progressive motor recovery at 8 mo	Able to eat and drink, speak, smell. Reduced chronic pain levels (8/10 pre-transplant, 1/10 post-transplant)	Self-appearance rating 3/10 pre-transplant, 7–8/10 post-transplant.	Objective improvement in depression, body image and quality of life. Anxiety and self-esteem levels remained constant
Lantieri (2)	Light touch – partial deep pressure sensitivity at 8 mo Heat/cold – absent at 17 mo	Recovery of orbicularis oris – 3 mo (right), 2 mo (left).	Complete mouth closure – 8 mo	Objective improvement in appearance	Objective improvement in quality of life. Return to employment at 18 mo
Lantieri (3)	Not yet reported	Not yet reported	Not yet reported	Objective improvement in appearance	Objective improvement in quality of life
Pomahac (1)	Light touch – 6 mo Heat/cold – 6 mo	Progressive recovery over 12 mo Symmetrical smile with 2–3 cm excursion of corners of mouth at 12 mo Motor control of transplanted upper lip at 12 mo	Speech and ability to breath and smell improved immediately post-op Ability for oral intake by 3d Unable to pucker lips at 12 mo	Assessed as excellent at 12 mo by team.	Accepted new face. No psychiatric events at 12 mo. Enhanced social capacity by 5 wks
Cavadas	Not yet reported	Not yet reported	Mandible excursion 10 mm at 16 mo Swallowing and starting phonation at 16 mo	Not yet reported	Not yet reported
Lantieri (4)	Light touch – absent at 12 mo Heat/cold - absent at 12 mo	Recovery of left zygomatic muscle – 5 mo Recovery of orbicularis oris – absent at 12 mo (right), 5 mo (left)	Complete mouth closure – 12 mo	Objective improvement in appearance	Objective improvement in quality of life
Devauchelle/ Dubernard (2)	Not yet reported	Not yet reported	Not yet reported	Pt satisfied at 20 mo	Not yet reported
Gomez Cia Barret	Not yet reported Recovery of total sensation in forehead, eyelids, cheeks intraoral mucosa at 4 mo. No sensory recovery in lips at 4 mo.	Not yet reported Active movement frontalis, lateral zygomatic muscles, upper orbicularis oculii at 4 mo. EMG showed motor reinnervation at commissures of mouth at 120d	Not yet reported Unrestricted mastocatory movement at 4 mo. Unable to close eyes fully at 4 mo	Not yet reported Pt satisfied at 4mo.	Not yet reported No psychological probs at 4mo.
Lantieiri (5)	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported
Pomahac (2)	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported
Pomahac (3)	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported
Lantieri (6)	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported
Lantieri (7)	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported
Pomahac (4)	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported

Abbreviation: EMG – electromyography.

has suggested that the donor's age should lie between 20 years below and 10 years above the recipient's age.[27] Skin mismatching or premature aging of the allograft have not been reported for patients thus far, but longer follow-up is required. The transfer of rosacea between donor and recipient[28] was observed in the seventh face transplant, identifying dermatological conditions of donors as additional selection criteria that should be considered in future face transplants.

4. Immunological outcomes

The working party reports estimated that 10% of facial allografts could fail as a result of acute rejection[2] and that, based on the hand transplant experience, episodes of acute rejection may be a common occurrence. To date, loss of a graft due to acute rejection has not been reported. As predicted, episodes of acute rejection have been frequent, occurring in almost all face transplants with follow-up reports and have been successfully controlled by increasing systemic immunosuppression (Table 3).[1,13,17,18,21–24]

The working party reports predicted that chronic rejection could affect 30–50% of facial allografts at five years.[3] Other teams were unable to quantify the risk of chronic rejection,[4,5] but raised concern over its potential effect on function of the allograft. The recipient of the first facial allograft is now in her fifth year following transplantation. An MRI scan performed at five years has shown no difference between the native and grafted soft tissues, with normal appearance of the vasculature.[25] Furthermore, there has been no clinical or histological evidence of chronic rejection in her or any other recipient. Currently over 70 composite tissue hand transplants have been performed and there has been one reported loss of a graft due to underlying intimal hyperplasia in the arteries, which may have resulted from chronic rejection.[29] It, therefore, seems that chronic rejection has had less of an impact than expected so far in composite tissue allotransplantation. Whilst the functional, aesthetic and psychological consequences of chronic rejection in facial transplantation have been modelled,[30] long-term follow-up of recipients is required to determine the clinical outcomes of this process.

The importance of tissue matching in facial transplantation could not be determined when the working party reports were written and still remains unclear. Episodes of rejection have been observed, despite extents of donor/recipient HLA matching. In addition, the number of acute rejection episodes observed has not correlated with HLA matching.[16,18,22,24] Long-term outcomes of the initial face transplants will help determine the significance of histocompatability matching, inevitably influencing the future selection of recipients and donors.

As expected, immunosuppression used in facial transplantation has been similar to that used in solid organ transplantation and hand transplants. Corticosteroids, tacrolimus and mycophenolate mofetil have been used in all patients with detailed reports (Table 3). Treatment with bone marrow infusion, thymoglobulin, anti-IL2 receptor antibodies, X-ray irradiation and phototherapy have varied between centres.

Adverse effects of immunosuppression include drug toxicity, opportunistic infections and malignancies.[31] The most serious of these side effects may result in conditions that shorten the life of the recipient. Risks posed to face transplant recipients by immunosuppressant therapy had, thus, historically been the subject of ethical debate.[8,31] Early reports predicted that the majority of face transplant patients could expect to experience immunosuppressant related side effects.[3,4] Follow-up of face transplants performed to date have described immunosuppressant side effects from drug toxicity and opportunistic infections, including impaired renal function, thrombotic microangiopathy, diabetes mellitus, cytomegalovirus and herpes simplex virus infection (Table 3).[1,17,21,23,24] These complications have almost all been successfully managed. The sixth face transplant recipient developed multi-resistant *pseudomonas aeruginosa* on post-operative day 15, affecting the facial graft, requiring tapering of the immunosuppression and surgical excision of the infected tissue.[18] An EBV related post-transplant B-cell lymphoma occurred in the second recipient of the Lyon/Amiens group. This affected the liver, spleen, pancreas, lungs and lymph nodes and was treated with rituximab, resulting in full remission.[32] The Valencia patient developed a pseudosarcomatous spindle-cell nodule at the base of the tongue on post-operative month 11.[33] This benign pseudotumour was removed surgically and there have been no reports of recurrence.

There had been optimism that protocols to induce transplant tolerance could be developed within the first few years of the face transplant programme.[3] However, this was not considered likely. In an attempt to induce transplant tolerance, bone marrow was transplanted with the first face transplant. Multiple assessments during the 18-month period following transplantation demonstrated haematopoietic microchimerism only on one occasion.

There have been two reported mortalities amongst the face transplant recipients.[34,35] The Chinese patient died 27 months following his transplant. A post-mortem to confirm the exact cause of death was not performed. However, it is believed that he discontinued his immunosuppression and consequently developed multi-organ failure.[36] The second reported mortality was the sixth recipient,[35] who received a facial myocutaneous allograft with concomitant bilateral below-elbow upper limb transplants. This patient experienced a cardiac arrest due to tracheostomy obstruction.[18] Following five weeks of intensive care therapy, the patient died on day 65 post-operatively.[18] This recipient developed areas of skin necrosis, related to multi-resistant *pseudomonas aeruginosa* infection, but several biopsies from the transplanted tissue were negative for immune-mediated rejection.[35]

5. Psychological outcomes

Potential psychological issues, raised in the initial medical literature on facial transplantation, included early post-operative distress,[11] communication difficulties,[2,11] feelings of depersonalisation towards the new face and avoidance behaviours.[11] In addition, it was thought that face transplant recipients might be prone to anxiety or depression due to the large number of stressors present such as the fear of graft viability or rejection, worry about immunosuppressant side effects, feelings of personal responsibility for the success of the graft linked to adherence of treatment regimes, identity transfer and emotional responses towards the donor.[2,3,11]

Identity transfer from donor to recipient had excited considerable lay interest, in part generated by the media. This was mentioned as a potential risk in the working party reports of The Royal College of Surgeons.[2,3] However, this concern was not shared by the scientific community involved in the development of facial transplantation. Thus far, no concerns regarding identity transfer have been reported amongst face transplant recipients.

Psychological outcomes in the fourth face transplant recipient have been evaluated quantitatively.[37] Measurable ratings of depression, body image, quality of life and societal reintegration showed improvements following facial transplantation. Scores measuring psychological distress rose at three months post-transplant, when the patient started socialising and then markedly fell. However, a subsequent rise in psychological distress was seen, which coincided with CMV infection. Measurement of teasing revealed that the patient suffered less teasing and verbal abuse, whilst receiving more positive affirmations from observers after the transplant.[37] Anxiety and self-esteem scores remained constant following the procedure.[37] Lantieri et al have described improvements in quality of life and appearance, measured quantitatively, in their first four recipients.[18] In addition, two of these patients have been able to return to employment.[18,21]

Although objective psychological assessment, using validated measures, has not yet been reported amongst the other face transplant recipients, favourable psychological outcomes have been observed. The first recipient of a face transplant was able to

Table 3
Immunological outcomes of facial transplantation.

Team	HLA Matches	Immunosuppression	Rejection episodes	Immunosuppression complications
Devauchelle/ Dubernard (1)	5/6	Induction – antithymocyte globulin, tacrolimus, MMF, prednisolone. Maintenance – tacrolimus, MMF, prednisolone. Bone marrow infusion d4,11.	2 (d18, 214)	Decline in renal function HSV lip infection Molluscum contagiosum Thrombotic microangiopathy Hypertriglyceridaemia Hypertension Bilateral bacterial pneumonia Mild cholangitis
Guo	3/6	Induction – prednisolone, MMF, tacrolimus, methylprednisolone, anti-IL-2 receptor MAb, Maintenance – tacrolimus, MMF, prednisolone (stopped at 22 mo)	3 (mo3, 5, 17)	Hyperglycaemia (d3) Diabetes mellitus (mo3)
Lantieri	3/6	Induction – antithymocyte globulin, tacrolimus, MMF, prednisolone Maintenance – tacrolimus, MMF, prednisolone,	2 (d28, 64)	Steroid induced confusion post-op CMV viraemia (d64)
Siemionow	2/6	Induction – antithymocyte globulin, methylprednisolone. Maintenance – tacrolimus, MMF, prednisolone	1 (d47)	CMV infection at 7 months Transient leukopaenia (wk2, mo6)
Lantieri (2)	1/6	Induction – antithymocyte globulin, tacrolimus, MMF, prednisolone Maintenance – tacrolimus, MMF, prednisolone	1 (d0)	*Pseudomonas aeruginosa* pneumonia (d2)
Lantieri (3)	2/6	Induction – antithymocyte globulin, tacrolimus, MMF, prednisolone Maintenance – tacrolimus, MMF, prednisolone	0	Multiresistant *pseudomonas aeruginosa* infection (d12-65)
Pomahac (1)	3/6	Induction – antithymocyte globulin, methylprednisolone, MMF Maintenance – MMF, tacrolimus, steroid taper	1 (d17)	Post-transplant diabetes Steroid bolus treatments given d74, 107. 3 courses of topical treatment given. Persistent facial redness attributed to rosacea transferred from donor.
Cavadas	0/6	Induction – basiliximab, tacrolimus, MMF, corticosteroids Maintenance – Tacrolimus, mycophenolate mofetil, prednisolone	2 (d14, 350)	Pseudosarcomatous spindle-cell nodule at base of tongue (mo11)
Lantieri (4)	2/6	Induction – antithymocyte globulin, tacrolimus, MMF, prednisolone Maintenance – tacrolimus, MMF, prednisolone	1 (d5)	HSV 1 infection of lips (d3-10)
Devauchelle/ Dubernard (2)	1/6	Induction – antithymocyte globulin, tacrolimus, prednisolone, MMF Maintenance – tacrolimus, prednisolone	5 (d41, 103, mo6, 16, 18)	*Staphlococcus aureus* and *Candida glabrata* in post-op phase. HSV 1 infection of graft (d6, 86, 160, 226, mo16) EBV related post-transplant B-cell lymphoma.(mo5)
Gomez Cia	Not yet reported	Induction – Basiliximab, tacrolimus, methylprednisolone Mainenance – Not yet reported	Not yet reported	Rhabdomyolysis (d1) with renal impairment (but not attributed to immunosuppression)
Barret	0/6	Induction – antithymocyte globulin, prednisolone Maintenance – tacrolimus, MMF, prednisolone	3 (d3, 28, 75)	No infectious complications reported at 4mo.
Lantieri (5)	Not yet reported	Not yet reported	Not yet reported	Not yet reported
Pomahac (2)	Not yet reported	Not yet reported	Not yet reported	Not yet reported

(*continued on next page*)

Table 3 (*continued*)

Team	HLA Matches	Immunosuppression	Rejection episodes	Immunosuppression complications
Pomahac (3)	Not yet reported	Not yet reported	Not yet reported	Not yet reported
Lantieri (6)	Not yet reported	Not yet reported	Not yet reported	Not yet reported
Lantieri (7)	Not yet reported	Not yet reported	Not yet reported	Not yet reported
Pomahac (4)	Not yet reported	Not yet reported	Not yet reported	Not yet reported

Abbreviations: HLA – human leukocyte antigen, MMF – mycophenolate mofetil, MAb – monoclonal antibody, CMV - cytomegalovirus.

face the outside world and start socialising by the twelfth post-operative week,[1] with psychological acceptance of the graft correlated to return of expressiveness. Eighteen months following transplantation, this patient was reported to be able to walk in the street and meet new people without any problems.[22] Despite the poor outcome eventually observed in the second face transplant, the patient accepted his new face easily.[17] No significant psychological issues were reported at one year in the seventh recipient of a face transplant.[24] This patient returned home five weeks post-operatively and was able to re-integrate into his community with enhanced social capacity. Favourable psychological outcomes have also been reported in two of the Spanish face transplant recipients.[13] Whilst publications in the medical literature are awaited, the last three face transplant recipients in Boston have been able to face the media and have reported encouraging psychological benefits.[38]

6. Discussion

Composite tissue allotransplantation of the face offers some clear advantages over other reconstructive methods. Unlike flaps and grafts, facial transplantation upholds the Gillies principle of “replacing like with like”. The intricate and visible structures of the face mean that transplantation can yield better functional and aesthetic results than reconstruction using conventional methods. However, facial transplantation remains controversial. Unlike cardiac, lung and liver transplants, facial allografts are not life-saving. Therefore, the decision for every patient considering this procedure is whether the life-enhancing benefits merit the surgical, immunological and psychological risks.

The initial success of facial transplantation is testament to the careful approach taken by the face transplant teams and the guidance set out by the American Society of Plastic Surgery[39] and the Royal College of Surgeons of England.[3] Thus far, surgical, functional and aesthetic, immunological and psychological outcomes have been very encouraging. Facial transplantation has conferred reduction in chronic pain levels and improvements to important functions such as smiling, smelling, eating, drinking and speaking. The impact of these changes on quality of life has been considerable and resulted in the reintegration of these patients into the outside world, social networks and even the workplace.

Despite the remarkable surgical success to date, continued refinement of technique is necessary to avoid the extensive blood loss seen in face transplants thus far.[17–19] Future teams must also have clear recovery plans in the event of failure, as described by Butler et al.[40]

The immunsuppression related side-effects observed in face transplant recipients to date have included malignancy and organ toxicity. This has highlighted that facial transplantation should be performed by an experienced multi-disciplinary team, including transplant immunologists. Based on the current experience, recipients should be matched for EBV status and given prophylaxis for opportunistic infections. The occurrence of these complications has also emphasised that facial transplantation should be limited to patients with the most severe aesthetic and functional deficits, for whom reconstruction with autologous tissue is not feasible.

Rejection is probably implicated in the mortality of the Chinese patient.[17] A similar problem was encountered at the start of the hand transplant programme, as the first allograft was rejected at 27 months.[41] These experiences demonstrate the importance of adherence to immunosuppressive regimens, which should be provided by the institutions undertaking the procedure. Thus, robust patient selection and support is the key predictor of successful outcome. Future face transplant teams must meticulously complete a rigorous patient-selection process.[42] In doing so, they can identify patients with realistic expectations who can comply with follow-up.

The second mortality following facial transplantation was in a patient that received concomitant facial and below-elbow composite tissue allografts.[35] The most recent facial transplant, performed in Boston also included concomitant bilateral hand transplants, which were subsequently removed.[38] It is important to note that failure of the hand transplants in this patient has not worsened their pre-operative status. The Boston team have also announced that this patient may be considered again for further hand transplants.[38] Siemionow et al have addressed the issues in concomitant face and hand transplantation.[43] Due to the complexity of concomitant transplantation and the limited experience of facial transplants, they have recommended staged reconstruction as the best option for the time being. Individual teams will need to evaluate the benefits and risks of concomitant composite tissue allotransplantation before deciding on treatment options.

7. Conclusions

The face transplant debate is similar to that which accompanied the development of solid organ transplantation. Renal and liver transplants are now well- accepted treatment options. However, the initial experience of both of these transplant programmes brought difficult challenges and frequent patient mortality.[44–46] By comparison, the early face transplant experience generally has been far more positive than predicted, although it is important to acknowledge that facial transplantation is not a life-saving intervention.

The early face transplant experience has demonstrated its feasibility as a reconstructive option. However, it remains an experimental procedure, which requires an experienced multi-disciplinary team. Dissemination of outcomes has allowed progress to be made, with teams performing more extensive procedures and considering a wider range of patients,[47] including an HIV positive recipient.[33] However, important information on functional outcomes and complications still remain outstanding. Face transplant teams should be encouraged to be transparent about their experiences. With this information facial transplantation may eventually become a first-line reconstructive option for patients with severe facial disfigurements.

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Author contribution

KS was the major contributor to writing of the manuscript and was involved with study design. SH and AC contributed to writing of the manuscript and study design. PB contributed to writing of the manuscript and was the major contributor in study design. All authors read and approved the final manuscript.

References

1. Devauchelle B, Badet L, Lengele B, Morelon E, Testelin S, Michallet M, et al. First human face allograft: early report. *Lancet* 2006;**368**:203–9.
2. Morris PJ, Bradley JA, Doyal L, Earley M, Hagan P, Milling M, et al. Facial transplantation: a working party report from the Royal College of Surgeons of England. *Transplantation* 2004;**77**:330–8.
3. Morris P, Bradley A, Doyal L, Earley M, Hagen P, Milling M, et al. Face transplantation: a review of the technical, immunological, psychological and clinical issues with recommendations for good practice. *Transplantation* 2007;**83**:109–28.
4. Petit F, Paraskevas A, Minns AB, Lee WP, Lantieri LA. Face transplantation: where do we stand? *Plast. Reconstr. Surg.* 2004;**113**:1429–33.
5. Siemionow M, Ozmen S, Demir Y. Prospects for facial allograft transplantation in humans. *Plast. Reconstr. Surg.* 2004;**113**:1421–8.
6. Hettiaratchy S, Butler PE. Face transplantation—fantasy or the future? *Lancet* 2002;**360**:5–6.
7. Butler PE, Clarke A, Ashcroft RE. Face transplantation: when and for whom? *Am. J. Bioeth.* 2004;**3**:16–7.
8. Butler PE, Clarke A, Hettiaratchy S. Facial transplantation. *BMJ* 2005;**331**:1349–50.
9. Agich GJ, Siemionow M. Facing the ethical questions in facial transplantation. *Am. J. Bioeth.* 2004;**4**:25–7.
10. Wiggins OP, Barker JH, Martinez S, Vossen M, Maldonado C, Grossi F, et al. On the ethics of facial transplantation research. *Am. J. Bioeth.* 2004;**4**:1–12.
11. Brill SE, Clarke A, Veale DM, Butler PE. Psychological management and body image issues in facial transplantation. *Body Image* 2006;**3**:1–15.
12. Clarke A, Butler PE. Facial transplantation: adding to the reconstructive options after severe facial injury and disease. *Expert Opin. Biol. Ther.* 2005;**5**:1539–46.
13. Barret JP, Gavalda J, Bueno J, Nuvials X, Pont T, Masnou N, et al. Full face transplant: the first case report. *Ann. Surg.* 2011;**254**:252–6.
14. Banks ND, Hui-Chou HG, Tripathi S, Collins BJ, Stanwix MG, Nam AJ, et al. An anatomical study of external carotid artery vascular territories in face and midface flaps for transplantation. *Plast. Reconstr. Surg.* 2009;**6**:1677–87.
15. Pomahac B, Lengele B, Ridgway EB, Matros E, Andrews BT, Cooper JS, et al. Vascular considerations in composite midfacial allotransplantation. *Plast. Reconstr. Surg.* 2010;**125**:517–22.
16. Siemionow MZ, Papay F, Djohan R, Bernard S, Gordon CR, Alam D, et al. First U.S. near-total human face transplantation: a paradigm shift for massive complex injuries. *Plast. Reconstr. Surg.* 2010;**125**:111–22.
17. Guo S, Han Y, Zhang X, Lu B, Yi C, Zhang H, et al. Human facial allotransplantation: a 2-year follow-up study. *Lancet* 2008;**372**:631–8.
18. Lantieri L, Hivelin M, Audard V, Benjoar MD, Meningaud JP, Bellivier F, et al. Feasibility, reproducibility, risks and benefits of face transplantation: a prospective study of outcomes. *Am. J. Transplant.* 2011;**11**:367–78.
19. Gomez-Cia T, Sicilia-Castro D, Infante-Cossio P, Barrera-Pulido F, Gacto-Sanchez P, Lagares-Borrego A, et al. Second human facial allotransplantation to restore a severe defect following radical resection of bilateral massive plexiform neurofibromas. *Plast. Reconstr. Surg.* 2011;**127**:995–6.
20. Hinojosa Perez R, Porras Lopez M, Escoresca-Ortega AM, Herruzo Aviles A, Leon A, Noval JA, et al. Severe rhabdomyolysis after allogeneic transplantation of facial structures: a case report. *Transplant. Proc.* 2010;**42**:3081–2.
21. Lantieri L, Meningaud JP, Grimbert P, Bellivier F, Lefaucheur JP, Ortonne N, et al. Repair of the lower and middle parts of the face by composite tissue allotransplantation in a patient with massive plexiform neurofibroma: a 1-year follow-up study. *Lancet* 2008;**372**:639–45.
22. Dubernard JM, Lengele B, Morelon E, Testelin S, Badet L, Moure C, et al. Outcomes 18 months after the first human partial face transplantation. *N. Engl. J. Med.* 2007;**357**:2451–60.
23. Siemionow M, Papay F, Alam D, Bernard S, Djohan R, Gordon C, et al. Near-total human face transplantation for a severely disfigured patient in the USA. *Lancet* 2009;**374**:203–9.
24. Pomahac B, Pribaz J, Eriksson E, Annino D, Catercon S, Sampson C, et al. Restoration of facial form and function after severe disfigurement from burn injury by a composite facial allograft. *Am. J. Transplant.* 2011;**11**:386–93.
25. Petruzzo P, Testelin S, Morelon E, Kanitakis J, Lengele B, Malcus C, et al. Outcome 5 years after the first human partial face transplantation. Paper presented at 15th Congress of the European Society for Organ Transplantation. 4–7 September 2011, Glasgow, United Kingdom.
26. Meningaud JP, Paraskevas A, Ingallina F, Bouhana E, Lantieri L. Face transplant graft procurement: a preclinical and clinical study. *Plast. Reconstr. Surg.* 2008;**122**:1383–9.
27. Aflaki P, Nelson C, Balas B, Pomahac B. Simulated central face transplantation: age consideration in matching donors and recipients. *J. Plast. Reconstr. Aesthet. Surg.* 2010;**63**:283–5.
28. Saavedra AP, Bueno EM, Granter SR, Pomahac B. Transmission of donor-specific skin condition from donor to recipient of facial allograft. *Am. J. Transplant.* 2011;**11**:1340–6143.
29. Kaufman CL, Blair B, Murphy E, Breidenbach WB. A new option for amputees: transplantation of the hand. *J. Rehabil. Res. Dev.* 2009;**46**:395–404.
30. Sivakumar B, Haloob N, Puri A, Latif A, Ghani S, Brough V, et al. Systemic sclerosis as a model of chronic rejection in facial composite tissue transplantation. *J. Plast. Reconstr. Aesthet. Surg.* 2010;**63**:1669–76.
31. Hettiaratchy S, Randolph MA, Petit F, Lee WP, Butler PE. Composite tissue allotransplantation—a new era in plastic surgery? *Br. J. Plast. Surg.* 2004; **57**:381–91.
32. Morelon E, Testelin S, Petruzzo P, Badet L, Michallet M, Dubois V, et al. Face transplantation and combined haematopoeitic stem cell infusion and vascularised bone marrow; first year of follow-up. Paper presented at 15th Congress of European Society of Organ Transplantation, 4–7 September 2011, Glasgow, United Kingdom.
33. Cavadas PC, Ibanez J, Thione A. Surgical aspects of a lower face, mandible, and tongue allotransplantation. *J. Reconstr. Microsurg.* 2011 [Epub ahead of print].
34. Gordon CR, Siemionow M, Papay F, Pryor L, Gatherwright J, Kodish E, et al. The world's experience with facial transplantation: what have we learned thus far? *Ann. Plast. Surg.* 2009;**63**:572–8.
35. Meningaud JP, Benjoar MD, Hivelin M, Hermeziu O, Toure G, Lantieri L. The procurement of total human face graft for allotransplantation: a preclinical study and the first clinical case. *Plast. Reconstr. Surg.* 2010 Jun 15.
36. Hui-Chou HG, Nam AJ, Rodriguez ED. Clinical facial composite tissue allotransplantation: a review of the first four global experiences and future implications. *Plast. Reconstr. Surg.* 2010;**125**:538–46.
37. Coffman KL, Gordon C, Siemionow M. Psychological outcomes with face transplantation: overview and case report. *Curr. Opin. Organ. Transplant.* 2010;**15**:236–40.
38. http://www.brighamandwomens.org/About_BWH/publicaffairs/news/facetransplant/facetransplantnash.aspx.
39. ASRM/ASPS. Facial Transplantation – ASMS/ASPS guiding principles. Available from: www.microsurg.org/ftGuidelines.pdf. Accessed August 3rd 2010.
40. Butler PE, Hettiaratchy S, Clarke A. Managing the risks of facial transplantation. *Lancet* 2006;**368**:561–3.
41. Petruzzo P, Lanzetta M, Dubernard JM, Margreiter R, Schuind F, Breidenbach W, et al. The international registry on hand and composite tissue transplantation. *Transplantation* 2008;**86**:487–92.
42. Clarke A, Butler PE. The psychological management of facial transplantation. *Expert Rev. Neurother.* 2009;**9**:1087–100.
43. Siemionow MZ, Zor F, Gordon CR. Face, upper extremity, and concomitant transplantation: potential concerns and challenges ahead. *Plast. Reconstr. Surg.* 2010;**126**:308–15.
44. Hamburger J, Vaysse J, Crosnier J, Auvert J, Dormont J. Kidney homotransplantation in man. *Ann. N.Y. Acad. Sci.* 1962;**99**:808–20.
45. Calne RY, Williams R. Liver transplantation in man. I. observations on technique and organization in five cases. *Br. Med. J.* 1968;**4**:535–40.
46. Starzl TE, Machioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddel WR. Homotransplantation of the liver in humans. *Surg. Gynecol. Obstet.* 1963;**117**:659–76.
47. Pomahac B, Diaz-Siso JR, Bueno EM. Evolution of indications for facial transplantation. *J. Plast. Reconstr. Aesthet. Surg.* 2011 [Epub ahead of print].