

## Prof. Mira Sen (Banerji) CME Article

# Vascularised composite allotransplants: Transplant of upper extremities and face

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## ABSTRACT

Transplantation of solid organs and bone marrow has become a highly acceptable and often the only available clinical solution in many situations. It has been practiced across the globe for quite a long time since the first kidney transplant in 1954. Transplantation of tissues other than these, which was termed composite tissue allotransplantation and currently as vascularised composite allotransplantation (VCA) is gaining acceptance as a solution for complex reconstructive problems. This involves the transfer of multiple types of tissue such as bone, muscle, nerve, skin and blood vessels. The advantage of these over the conventional reconstructive methods is its ability to give aesthetically and functionally superior equal composite substitute to the missing or deformed part. The composite tissues transplanted commonly include the upper extremities, face and abdominal wall. Among these, hand transplants were the first to be done and have been carried out more than any other VCA. This article reviews the current scenario of VCA especially of the hand and face, in the light of experience of the two bilateral hand transplants done recently in India.

## KEY WORDS

Face transplant; hand transplant; vascularised composite allotransplantation

## HISTORICAL PERSPECTIVES

The first successful organ transplant was performed at Boston in 1954 by a team led by a Plastic Surgeon Joseph E. Murray along with John P. Merrill and J. Hartwell Harrison. This was carried out on identical twins and hence did not need immunosuppression.<sup>[1,2]</sup> The use of homologous flexor tendon mechanisms in humans after animal experiments by Peacock was the first successful 'composite tissue allograft'.<sup>[3]</sup> The first

hand transplant in which immunosuppression was used, was performed by Gilbert in Ecuador in 1963. Unfortunately, the hand survived only for 3 weeks due to the inadequate immunosuppression. The immunosuppressants used were azathioprine and prednisone.<sup>[4,5]</sup> The discovery of cyclosporine in 1976 gave a boost to organ transplantation, as an

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effective immunosuppression being available. In 1998, the first successful hand transplant in the modern immunosuppressant era was performed in Lyon, France.<sup>[6]</sup> Since then, over 150 vascularised composite allotransplantation (VCA) procedures have been performed worldwide including more than 80 upper limbs and 24 partial/complete faces. There have been reports of abdominal wall, tongue, larynx, penis, bone and joint transplants and recently that of combined skull and scalp. The experience with hand and face transplantation has been encouraging with long-term success reported in most of the cases.

## **BASIC IMMUNOLOGIC CONSIDERATIONS IN COMPOSITE TISSUE ALLOTRANSPLANTATION**

### **Rejection of allotransplants**

Recognition and rejection of the allogeneic tissue by the recipient's immune system (alloimmune response) remains the main barrier to successful transplantation. ABO (blood group) antigens and the human leucocyte antigens (HLA) initiate these immune responses. HLAs are cell surface glycoproteins encoded by the major histocompatibility complex located on chromosome 6. HLA class 1 antigens (HLA-A, HLA-B and HLA-C) are expressed on all nucleated cells. HLA class 2 antigens (HLA-DR, HLA-DP and HLA-DQ) are expressed on antigen presenting cells (APCs) such as B lymphocytes, monocytes, macrophages, dendritic cells, endothelial cells and activated T cells. HLA and ABO antigens determine the compatibility of transplants.

APCs present the 'non-self' antigens to the recipient T-cells and activate them. T-cell response is central to the pathogenesis of transplant rejection. T-cell activation can occur directly (donor APC's migrate to host lymphoid tissue and activate recipient T-cells) or indirectly (recipient APCs process donor antigens and present them to T-cells). The indirect pathway is of greater significance in the pathogenesis of graft rejection.

Unlike a solid organ transplant, heterogeneous tissues in composite tissue allotransplantation express different amounts of MHC antigens and hence elicit a stronger degree of host immune response. In general, skin and bone marrow are rejected earlier and more aggressively than muscle, cartilage, tendon, nerve or bone.<sup>[7]</sup>

After the transplantation the immunologically active cells could be of donor or recipient origin which recognises the non-self-antigens. The immune reaction following this could result in the host versus graft reaction (commoner) or the graft versus host reaction which is rather uncommon in VCA. The resultant immune responses lead to mainly two types of rejection in the acute and the chronic rejections. These rejections can be either cellular mediated or antibody mediated.

### **Immunosuppression protocols**

Immunosuppression protocols are not standard in the various VCA programme across the world. These protocols are similar to that used in solid organs and rely on the two-phase induction and maintenance regime. The induction phase aims at depleting the T-cell and B-cell population, as well as to suppress, the antibody responses at the time of transplantation, when the immune load is at the maximum. The maintenance phase is to prevent the acute and chronic rejections throughout the lifespan of the transplant. The induction regimes mostly depend on using polyclonal anti thymoglobulin (ATG) or monoclonal agents such as Basilixumab and Alemtuzumab. Steroids play an important role in the induction, maintenance, as well as addressing the rejection episodes; the maintenance regime deploys steroids along with tacrolimus (calcineurin inhibitors) and mycophenolate mofetil (MMF) (antimetabolite). The pattern of steroid use is variable in different regimes, with an effort by many to reduce the amount or totally wean them off in the long term. Sirolimus has been used by some to wean the patients from tacrolimus with the aim to reduce the renal toxicity associated with the latter. The recent research looks at the possibility of inducing tolerance to reduce the amount of immunosuppression needed. Notable in this, is the Pittsburgh protocol in which infusion of donor vertebral bone marrow was used allowing a tacrolimus monotherapy for maintenance.<sup>[8,9]</sup>

Monitoring for rejections and managing them is important to have a successful outcome of allotransplantation. In fact, the majority of the hand transplants that have failed, may have had some non compliance in the long-term maintenance of the immunosuppression protocol. The advantages of VCA over solid organ transplants are the skin acts as a visible marker for detecting the rejections. Of the tissues included in the VCA the skin evokes the most antigenic response. The rejections could be cell-mediated or antibody-mediated. The cell-mediated rejections are common in the early phase and are

dominated by lymphocytic infiltration and the skin is the target organ. The skin changes are characterised by erythema and vesiculation of the skin. The skin biopsy shows an initially perivascular infiltration by lymphocytes with rejection at its extreme showing epidermolysis. The antibody-mediated rejection is characterised by microvascular injury and tissue destruction. They are detected by immunohistochemical methods. In general, the cell-mediated rejections are treated by increasing the immunosuppressant doses, bolus doses of methyl prednisolone or ATG. The cell-mediated rejections could be in addition reversed by agents like rituximab.

Chronic rejection occurs due to a long-term immunologic rejection response to the tissues. In solid organs, lot of factors have been implicated as the reason for chronic rejection. These include repeated acute rejection episodes, higher antibody levels of the recipient, prolonged cold ischaemia and non-compliance to immunosuppression. This has not been extrapolated to VCA due to the smaller number and the lower follow-up period in the VCA. In hand transplant, the deep major vessels can also be the target of the pathologic changes, which was cited as the cause for chronic rejection in one case.<sup>[10]</sup>

### Monitoring rejection

The rejection episodes are monitored by skin biopsy from the transplanted area. These are done on a protocol basis at frequent intervals initially and also when there is clinical suspicion of rejection. These biopsies, in fact help to detect rejections sufficiently early and allow their successful management in the skin containing VCA. During the time of transplant, some centres transplant a free flap like radial forearm into a less conspicuous area which serves as the biopsy site. This becomes important in face transplants, to avoid repeated scarring of the facial skin for the biopsy.

The histologic features of the skin biopsy have been codified by consensus meetings culminating in the BANNF grading for rejection.<sup>[11]</sup> The histological findings are graded as follows:

- Grade 0: None — Rare inflammatory infiltrates.
- Grade 1: Mild — Mild perivascular lymphocytic and eosinophilic infiltrates. No involvement of overlying epidermis.
- Grade 2: Moderate — Moderate to severe perivascular inflammation with or without mild epidermal and/or adnexal involvement.

- Grade 3: Severe — Dense inflammation and epidermal involvement with epithelial apoptosis dyskeratosis and/or keratinolysis.
- Grade 4: Necrotising acute rejection — Necrosis of single keratinocytes and focal dermal-epidermal separation.

## ISSUES WITH IMMUNOSUPPRESSION

The main criticism against VCA has been issues associated with immunosuppression. Although solid organ transplants are lifesaving, the VCA are non-vital and are done to enhance the quality of life, except in the transplant of abdominal wall along with intestinal transplants where closure of abdominal wall is not possible. The common complications of immunosuppression are opportunistic infections and systemic complications. Infections include cytomegalovirus, clostridium difficile enteritis, herpes simplex, cutaneous mycosis and osteomyelitis. The metabolic complications include hyperglycaemia, diabetes, hyperlipidaemia, hyperparathyroidism, Cushing syndrome, osteonecrosis and impaired renal function.<sup>[12]</sup> The quantity of skin and tissue being transplanted might have an influence in the complications associated with transplantation. Attempts to transplant two upper extremities and a lower extremity in a single operation resulted in the removal of the lower extremity in the early post-operative period. Moreover, there was a death reported 3 days after an attempted quadruple limb transplant.<sup>[13]</sup>

Most transplant programmes incorporate prophylactic antimicrobial therapy and surveillance for metabolic disorders and malignancies. Malignancies though reported in renal transplant patients are uncommon in VCA. One case of lymphoproliferative disorder in a lower limb transplant and skin cancer in another have been so far reported. Prophylactic antimicrobial therapy is a part of the drug regime and this includes valgancyclovir 900 mg/day for 6 months against cytomegalovirus and co-trimoxazole 400 mg/day for 6 months against *Pneumocystis carinii*.

## HAND TRANSPLANTS

The first-hand transplant of the modern immunosuppressive era was carried out in Lyon in 1999<sup>[6]</sup> and the second one in Louisville in 1999.<sup>[14]</sup> The first transplant was a unilateral transplant on a patient whose

compliance for the post-operative immunosuppression, and rehabilitation regime was poor. This resulted in its amputation after few years on request. The second-hand transplant patient till date has been successful, making the patient the longest surviving transplant of a VCA. The patient has been rehabilitated into normal activities and life. Since then more than 90 transplants have been done worldwide, including the 72 listed in the international hand transplant registry. The level of transplant has been in the majority, at the forearm/wrist level. The number of upper arm transplants has been less.

## ETHICAL ISSUES

The use of a treatment modality with known life-shortening complications while other safer rehabilitation methods are available has been one of the ethical issues debated in hand transplantation. The alternatives for rehabilitation include conventional reconstructive surgery or prosthetic limbs. Whereas the former plays a limited role, advances in prosthetic limbs have been tremendous. These include better neural-control interfaces, devices having terminals with multiple-degrees-of-freedom and haptic feedback mechanisms.<sup>[15,16]</sup> However, the acceptability of these prosthesis is still not high. The users of these prosthesis complain about its weight, absence of tactile feedback, and the cumbersome nature of wearing it for a long time.<sup>[17,18]</sup> After the successful transplant in our centre, we have had several patients coming to us enquiring about the feasibility of hand transplants. Among them are a few already using the myoelectric prosthesis. The common reason put forward by them for being dissatisfied with the use of prosthesis was the inability to use for day to day activities specially the activities needing close contact with water. Hence, considering the risk to benefit ratio, it might be justifiable for a bilateral amputee to be offered a bilateral hand transplant as a rehabilitative measure. In fact, several centres list hand transplant as the standard of care for bilateral amputees. In cases of unilateral amputee this may not be true. At our centre, when we started the programme we had considered several factors before we decided to whom to offer hand transplants. These factors included lack of available information on the effect of immunosuppression in VCA in the Indian population, our inexperience and concern about the lack adequate social support for lifelong immunosuppression. Hence, we decided to embark on hand transplant only in bilateral amputees, till further evidence for the superiority of benefit over risk emerged

for implementing it in unilateral amputees. Preliminary social and psychological assessment in bilateral amputees prior to listing for transplantation revealed a profound effect of the amputation in their day to day living.

## DONOR AND RECIPIENT SELECTION

Recipients for hand transplants should be carefully screened and selected. The indications are not yet well defined, but include bilateral and unilateral amputations. The level of amputation if in the wrist and forearm has been generally preferred, but arm transplantations have been done with a successful outcome. The American Society for Reconstructive Transplantation (ASRT) has put forwards guidelines<sup>[19]</sup> in the selection of patients fit for consideration of the upper extremity transplants. The group which is to be excluded is:

- a. Unilateral amputee with no functional, social or financial impairment
- b. Congenital deformities—currently no clear evidence is available about the neural plasticity which may allow return of functions
- c. Paediatric amputees — the available information does not justify the risk benefit in the paediatric population for the prolonged immunosuppression along with the ethical conflicts in proceeding with it with parental consent alone.

The final outcome of hand transplantation depends a lot on patient factors. Apart from the compliance to lifelong immunosuppression with its associated medical and financial implications, a serious commitment to the hand therapy regime is essential. Even in solid organ transplants compliance to medications is a problem, in spite of the fact, that the successful outcome is essentially lifesaving. Hence repeated detailed psychosocial counselling and preparation is essential before a candidate is accepted into the programme. The social support available should be verified to the satisfaction of the transplant team. In our case, the team leaders had made several visits to the home and the community of the first recipient to assess the support and, as well as sensitise the local community.

In general, a prior period using myoelectric prosthesis has been advised before the candidate is accepted into the programme. This has been suggested by the ASRT in its guidelines.<sup>[19]</sup> However, the availability and its relative high cost can be a deterrent to use this in our population.

Our first transplant patient was offered the same, but declined it after trying it out.

## DONOR SELECTION

Deceased donors for VCA are more difficult than that for solid organs. This might not be a great problem in the western population where organ donation after brain death has been in vogue for several decades. The concept of deceased person organ donation is only catching up in the Indian subcontinent and lags way behind other countries even in the donation of solid organs. The donation of externally visible organs such as face and hands is still a difficult subject to discuss with the families at the time of counselling. In our cases, discussing the functional issues faced by the probable recipients, as well as showing, the family the prosthetic limbs to be fixed after donation helped.

HLA matching and compatibility testing have been practiced differently in various centres.<sup>[20]</sup> The matching has generally been similar to that adopted in kidney transplants. The common methods available are flow cytometry, virtual cross matching, complement dependent cytotoxicity and Luminex assay. The tissue for matching has been donor lymphocytes either from the peripheral blood or the lymph nodes harvested, usually from the inguinal region. Cross matching using peripheral blood carries the risk of false negatives in donors who have had multiple blood transfusions. The antigenic responses of the lymphocytes may be altered due to the prior brain death status of the donor, which may reflect on the matching.<sup>[21]</sup> In spite of this, majority of the centres carrying out VCA, including ours use the peripheral blood than lymph nodes due to logistic reasons.

## IMMUNOSUPPRESSION REGIMENS IN HAND TRANSPLANT

Both ATG or agents such as basiliximab (interleukin-2 receptor blocker) or alemtuzumab (anti-CD52 monoclonal antibody) has been used for induction. There is a trend towards using agents other than ATG by different groups. The Innsbruck report of the four cases states that they used ATG for first two cases, and alemtuzumab in the next two.<sup>[22]</sup> The Louisville group initially used basiliximab for first 2 patients as induction agent but later on used alemtuzumab. The maintenance immunosuppressive

regimen commonly used has been triple regime comprising of low-dose steroid with tacrolimus and MMF. However, some teams to wean off tacrolimus to limit the nephrotoxicity have used sirolimus. We depended on ATG induction along with methyl prednisolone and triple regime immunosuppression in both our cases. Topical medications such as tacrolimus and steroid creams sometimes can be utilised to treat acute cutaneous rejection, reversing or preventing rejection episodes with minimal systemic effects.<sup>[23]</sup>

## REHABILITATION

The rehabilitation protocols used vary between centres, and mostly reflect the protocols used for rehabilitation of replanted hands. In principle, they are all aimed at providing splintage for the initial days along with passive movements followed by active movements to provide tendon gliding and muscle strengthening. The patient receives physical therapy up to 3-6 h a day for 5 days a week. From the second post-operative week onwards, the patient is progressively encouraged to engage in activities of daily living. Electrical stimulation of the muscles is started during the 2<sup>nd</sup> month to strengthen them. The rehabilitation measures continue under supervision for at least 1-year depending on the recovery, patient compliance and reliability.

## DOCUMENTATION AND ASSESSMENT OF RESULTS

The International Hand and Composite Tissue Transplantation (IRHCTT) were founded in 2002 with the main purpose of acting as a body to collect information from each case of vascularised composite allotransplantation. The registry allows to analyse the experience so far, and keeps updating regarding what is new happening in this field.

The IRHCTT has its own functional scoring system — Hand Transplant Scoring System (HTSS). The system has six domains that are, appearance, sensibility, movement, psychological and social acceptance, daily activities and work status and patient satisfaction. Based on the HTSS scale, the majority of patients' demonstrated good results from the hand transplant procedure. All the 31 patients analysed at 1-year developed protective sensations, and 90% had tactile sensibility. The recovery of motor function was very good in the larger muscle



groups but was variable in intrinsic muscles. However, all the patients were able to perform most daily activities in 1-year time and most of them returned to work. The Disabilities of the Arm, Shoulder and Hand (DASH) score is another common modality used by all centres for evaluating the outcome. The DASH Outcome Measure is a 30-item, self-report questionnaire, designed to measure physical function and symptoms in people with any of several musculoskeletal disorders of the upper limb. This measures the function of all major joints of the upper extremity. All the patients have reported improvement in DASH score with initial years this being more marked than later years.<sup>[24,25]</sup> As may be expected, absolute gains were more significant in patients receiving bilateral transplants than those receiving a single extremity.

## FACE TRANSPLANT

The team led by Dubernard in Amiens, France did the first partial face allotransplantation in 2005. A full face consisting of soft tissue and bony structures, was performed by a team led by Barret *et al.* in Barcelona, Spain in 2010.<sup>[26,27]</sup> To date, over 35 facial allotransplantations have been reported from France, USA, Spain and China. Unlike hand transplantation, facial transplantation has got more issues of concern to be addressed. Ethically the legal and social concerns on the identity are not clear in many countries including India. Technical difficulties also could be more than that of hand transplants, where the anatomy is simple and experience acquired with replant helped a lot. The availability of large mucosal areas which may be a target area for host rejection responses is added worry since this may be areas for microbial onslaught after mucosal aberrations.

A systematic review by Smeets *et al.* in 2014<sup>[28]</sup> on the published reports of face transplants gives an interesting insight into the behaviour of these transplants. A total of 36 articles published till 2013 reported 27 worldwide face transplantations. Ten of the 27 cases were full face transplants, and the remainder were partial face transplants. There was no report of graft loss, hyperacute (within the first 48 h) or chronic rejection or graft-versus-host disease. However, all of the patients during their 1<sup>st</sup> year post-transplant had at least one episode of acute rejection. The main complications as in the case of hand transplants were related to immunosuppressive therapy, leading to opportunistic infections, metabolic disorders, and increased incidence of malignancy. There

have been three reported cases of malignancy to date. There were three deaths in transplant recipients. The reasons were an infection due to lack of compliance with immunosuppressive therapy, multidrug-resistant infection and graft necrosis, and recurrent cancer. The review reported that functional recovery was good with, tactile sensitivity recovering in a mean of 4.1 months after surgery when nerve repair was performed, and a mean of 7.3 months otherwise. With nerve repair, temperature sensitivity recovered a mean of 4.3 months and this happened in a mean of 12.5 months if sensory nerves were not repaired. Motor recovery began a mean of 7.8 months after surgery. The first face transplant recipient was able to fully open her mouth, smile, speak, chew and swallow after 5 years of follow-up. Furthermore, in 2014, Fischer *et al.* in 2014<sup>[29]</sup> reported the functional outcomes in five patients treated at their centre. Each patient's pre- and post-surgical functioning was compared. All five patients had compromised respiration, breathing, sensation and facial expression before surgery which showed substantial recovery after surgery. The five patients were able to breathe through their noses after the surgery and tracheostomy could be decannulated in two of them who had it prior to the surgery. Sensory recovery started by 3 months and light touch and temperature sensitivity came to some extent by 3-9 months. All patients showed recovery of facial expression, including the ability to smile, all patients were capable of oral food intake 3-29 days after surgery, and 3-12 months after surgery, all had unrestricted or nearly unrestricted eating and drinking. With two patients even reporting regaining of their lost smelling power to some extent. They reviewed the results of 24 face transplants reported so far and found that all had bettered smelling eating and sensory capabilities and all patients who required gastrostomy and 91% of patients depending on tracheostomy were decannulated.

## FUTURE OF VASCULARISED COMPOSITE ALLOTRANSPLANTATION PROGRAMME IN INDIA

The first two hand transplants done in India were challenging tasks to undertake. Both were double hand transplants and needed a large team to make it succeed [Figure 1]. The logistics of arranging four operation theatres with the surgical teams synchronously working, managing the patients in the immediate post-transplant period, managing the immunosuppression and its



Figure 1: Amrita hand transplant team

attendant problems and instituting proper rehabilitation measures was all daunting tasks. However, more than these, the logistics of preparing the centre, obtaining the statutory authorisations, counselling the patients, choosing the right recipients, and above all procuring suitable hands from deceased donors was more daunting. In spite of these, the immediate successful outcome, the excellent compliance of the recipients and the return of function as would have been expected has given a good start to the VCA programme in the country. These transplants have brought in a welcome attention to the deceased donor organ donation drive in the country. With the public attention being focussed on these transplants there has been great demand for hand transplants from different parts of the country. The functional recovery in face transplants, as discussed earlier is very good and may be a boon to a large number of patients in the country with grossly deformed and functionally compromised faces. A lot of other tissues are reported to be transplanted successfully in different parts of the world. These include abdominal wall along with intestinal transplants, penis, uterus, trachea and skull with the scalp. With such rising expectations come the added responsibilities the VCA programme faces in the country. However, for moving forwards in this lot needs to be done which includes sensitising the public and the health policy makers on various aspects of VCA programme. The programme is to be judiciously implemented elsewhere in the country in well-equipped centres maintaining high ethical standards. The legal issues related to the transplant act needs to be addressed. The recent amendments to transplant act have brought in a lot of welcome changes in the law related to deceased organ transplants. Although, the role for VCA that is, the hands and face have not been defined it which needs to

be looked into. Research in the field of VCA is virtually absent in the country and needs to be taken up vigorously to look at the needs and peculiarities pertaining to our population. This will enable us to embrace the technique of VCA as a tool for reconstruction and rehabilitation. As expressed succinctly by Murphy *et al.*<sup>[13]</sup> a balance must be achieved between the quality of life gained from VCA and the quantity and quality of life lost from the complications of the procedure and the necessary lifelong immunosuppression.

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