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HAND TRANSPLANTATION: THE GIFT OF HANDS

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ABSTRACT

Complex injuries to the upper extremities result in structural, functional and aesthetic deficits. Hand transplantation is a vascularized composite tissue allotransplantation with complex technical and immunologic challenges. The knowledge of hand transplantation is still evolving even after many successful procedures. Long- term immunosuppression with associated costs and complications are the real challenges in Hand transplantation and needs careful attention and consideration. Components of transplant program consists of protocols for donation of upper extremity, receipt selection for transplantation, surgical techniques, and immunosuppression. Ethical issues and financial considerations must be addressed well in advance to avoid complications and they are crucial for the success of the procedure. Post-operative rehabilitation, nerve regeneration are the important criteria that decide the final functional outcomes.

INTRODUCTION:

Hand transplantation improves quality of life in patients with amputation of hands and is not considered a lifesaving procedure. It has numerous direct beneficial effects of restoration of function, sensation and appearance. Indirect benefits of hand transplantation are improved socialization, reduced stigma related to limb loss, and greatly improved quality of life.[1] Trauma due to motor vehicle or industrial accidents, congenital birth defects are the common causes of loss of limb. Systemic diseases like cardiovascular diseases, diabetes mellitus, and osteo-sarcoma also contribute to loss of hand and upper extremity due to amputation procedures. It is associated with psychosocial and economic issues due to loss of working days and reduced income for the family. Composite tissue transplantation of the hand has enhanced the quality of life of many recipients. Availability of immunosuppressive agents with greater efficacy and less side have achieved good results in hand transplantation procedures. An Austrian with bilateral hand transplantation returned to his work as police officer and the first American hand transplant recipient continues his work as an emergency medical technician (EMT) instructor. These outstanding examples prove the benefits of the procedure that improves the psychological, economic and social aspects of life in these patients.

Dr.Peter Medawar, a British biologist defined the immunologic mechanism of allograft skin rejection and was awarded the Nobel prize. Dr Earle Peacock, University of North Carolina coined the term Composite Tissue Transplantation and performed the first non-vascularized CTA of a finger flexor tendon apparatus in 1957. Composite Tissue Transplantation (CTA) is "transfer of vascularized or non-vascularized heterogeneous tissues such as skin, fat, bone, muscle, nerve with different antigenicities from one person to another".[2] Hand transplant is most immunogenic and complex compared to other organ or tissue transplant; considered the **"Gold standard"** in CTA as it involves multiple tissues like skin, muscle, tendon, bone, fat, cartilage, nerves and blood vessels.

International Registry on Hand and Composite Tissue Transplantation (IRHCTT), has as on May 2017, registered 66 cases of upper extremity Transplantations (UET) with18 unilateral and 38 bilateral procedures. 30 face allotransplantations (FT) were also registered. Patient survival rate following upper extremity transplantation has been identified as 96.7% at one year, 5years,and 10 years follow up after transplantation; The graft survival rate was 90.4% at one year and 86.6% at 5years and 10 years following the procedure. Allotransplantation of face patient survival was 96.6% at one year and 96.2% at 5 years with graft survival at 96.6% at one year and 5 years follow up and final outcome of procedures were satisfactory in majority of the recipients. Scalp, larynx, femur and penis are the possible composite tissue transplantations being done across 13 countries. Hand transplantation procedure are more complex and difficult compared to other organ transplantations. ***Approximately 100 hand transplantations have been performed on more than 60 patients as of 2017.*** The first successful hand transplant (1999) in Louisville, Kentucky, remains the longest surviving for 19 years since transplantation.[3]

History of the procedure:

Hindu mythology has the story of Lord Shiva replacing severed head of Ganesha with the head of one of his Ganas. Cosmos and Damian, Arab physicians transplanted a black leg of an Ethiopian to white body of the patient. Historic mention of limb transplantation dates back to 348 AD. Milestones in the development of Hand transplantation are:

Table.1 History and milestones in Hand Transplantation

Year	Procedure done	Final outcome
1964	The first scientifically documented attempt at hand transplantation took place in Ecuador	Lack of proper immune-suppression led to rejection. Transplanted hand was amputated 2 weeks later.
1996	Louisville Hand Transplant Team was established	
Sep 23, 1998	Human hand transplantation in Lyon, France for a right-handed amputee patient was the first short-term success in the procedure.	He did not comply with immunosuppressive regimen and the trans-planted limb was removed 29 months later
January of 1999	First official hand transplantation at Louisville achieved a long-term success, the recipient was a 37-year-old man.	
January13, 2000	Dr. Jean-Michel Dubernard of Lyon, France did the **world's first double hand transplant**	
May, 2000	China has been credited for the **first female hand transplant**.	
May 2000	World's first successful hand and arm transplant was done in Malaysia. One month-old girl received the hand from her deceased identical twin.	
April 30, 2003	Second bilateral hand transplantation in Lyon, France	

In November 2006,	Ground breaking steroid-free protocol using alemtuzumab (Campath) was used for the first time in a successful hand transplant in a 54-year-old man by the Louisville team.	Campath is a monoclonal antibody, administered in a single dose preoperatively to produce lymphocyte depletion, without steroid maintenance therapy afterward.
July 2008,	**First double arm transplant was done** in Munich, Germany. The procedure had 3 episodes of rejection in the first 6 months following surgery.	Patient had 2 years of extensive physiotherapy. Full range of elbow, wrist and finger movements were documented. Was able to use both hands during daily activities.
July 2008	The American Society for Reconstructive Transplant Surgery.	
March 2009	Bilateral hand and face transplant was performed in Paris.	Death resulted from infectious complications related to the face transplant.
27th Dec, 2012	First HT in UK done for right hand (51 years old male patient) affected with Gout	
3rd July, 2014	VCAs were added to the list of defined organs	
July 2015	Zion Harvey became the world's first child to have bilateral hand transplant.[4]	
Sep.2018	First women in UK to have a double hand transplant	

History of Hand Transplantation in India:

India's first ever hand transplant was done at Amrita Hospital, Kochi in January 2015. The recipient was a 30-year-old patient. Another hand transplant surgery also at the wrist level was performed successfully on a young Afghan soldier in April 2015.[5] In July 2016, India's first double transplant at the elbow level was performed. All these procedures were successful and patients were able to get back to their jobs and integrate well into the society.

Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry (JIPMER), performed its first cadaveric hand transplantation surgery on August 2nd 2017. JIPMER is the first government institution in the country to achieve this milestone, performed the 16 hour long surgery to transplant both forearms and hands from 50 year old donor to a 16 year old bilateral below-elbow amputee. The first dual hand transplant in Tamil Nadu was done at Government Stanley Medical College and Hospital, Chennai on February 7, 2018. The surgery on a 29-year-old male patient lasted for 13 hours and regular follow up shows improvement with no signs of rejection episodes.

Hand transplantation Vs Prosthesis:

Loss of upper limb is associated with major psycho-social impact on the individual's aesthetic and functional aspects. Main concerns are social and economic with loss of working days and associated psychological concern to get back to regular job. Hand transplantation poses great challenges starting from patient selection and extends till the rehabilitation processes are complete. The challenges include financial burden, risks of immunosuppression, functional outcomes and effect on quality of life. ***Transplanted limb has the advantages of improved appearance, functionality and sensation compared to the prosthesis.***[6] The recipient has positive psychological impact by the appearance of a normal hand. Prostheses cannot reproduce intricate actions of a native hand and transplanted hand is functionally a superior option. Transplanted hands provide superior dexterity of movement, sensation, associated intrinsic muscle function, and proprioception. They provide size and colour match and overall improved appearance. Return of protective sensation in 90% of recipients is a valuable aspect that cannot be achieved even by most advanced myoelectric prostheses. The financial burden and complications secondary to the life-long immunosuppression are vital factors to be considered.[7]

INDICATIONS:

Patients who have undergone above wrist but below elbow level amputation procedures of one or both hands are candidates for single or bilateral hand transplantation.[8] Amputation of the dominant hand or patients with bilateral below elbow amputation are also important indications for hand transplantation. Recipients must be screened thoroughly for good health and ideally aged between 18-65 years. Children are not ideal candidates for hand transplantation. Patient selection of children and those with congenital hands are based on the growth potential of the transplanted hand. They have greater surgical risk due to smaller size of limbs and microscopic size of blood vessels. Before the procedure the amputee must be detailed regarding the possible complications and expected functional outcome of the trans-planted hand. Clinical Policy bulletin for hand transplantation procedure must be framed.[9] Bilateral above-elbow transplantation was successfully performed for first time in Munich, Germany, in July of 2008. The decision to proceed with bilateral above-elbow transplantation was made by the recipient on his own. Indications for above-elbow amputees are still being debated. Better and reliable outcomes and functional recovery are anticipated in younger patients with amputation below the elbow, compared with older patients with multiple comorbidities.[10]

Protocols for inclusion and exclusion criteria for hand transplant program are framed by hand transplant centres on their own.

Inclusion criteria: Patients aged between18 to 69 years are ideal candidates. Recipient should not have any medical condition that may have negative implication on immunologic, surgical or functional aspects of the transplantation. The patient should not have psychosocial issues and must be thoroughly screened. Patient must be fit to give consent on his own for cell collection, storage and bone marrow infusion procedures. He must be free from cancer in past 10 years and should not have HIV infection. A period of greater than six months since injury to the extremity with attempt at rehabilitation is an important criteria.

Exclusion criteria: Patients in the age group below 18 or greater than 69 years are not ideal candidates. Other contraindications include presence of chronic infections, malignancy, any condition with lowered immunity. Patients with coagulopathies, connective tissue, vascular or hematologic disease are excluded. Patients with metabolic, genetic bone diseases, Lipopolysaccharidosis and amyloidosis are considered contraindications. These basic guidelines are followed by several USA hand transplant centres.

Regional organ procurement organization has issued **exclusion criteria** guidelines for **hand donor**. Patients with untreated sepsis, active tuberculosis or presence of malignancy are not suitable donors. Presence of Human immuno-deficiency virus (HIV), active cytomegalovirus, Epstein-Barr virus, viral hepatitis B or viral hepatitis C, viral encephalitis are excluded. Rule out current intravenous drug use and tattooing within the recent past six months.[11,12] Patients with systemic or limb-related neuropathies, presence of rheumatoid arthritis and osteoarthritis are also

excluded as donors.

Hand transplantation must be considered very judiciously in patients below 18 years of age and greater than 65 years. Transplantation performed successfully to a child from identical twin did not require immunosuppression and this factor has been removed from the ethical considerations. **The ideal donor** must be aged between 18-65 years. Matching is done for gender, race and age. Skin tone, and size of the limb (must be within 15% of recipient size) must be ascertained. Viral status and blood type must also checked before the procedure and make sure the donor was not on excessive vasopressor drugs to maintain blood pressure just before retrieval of the hand.

Ethical issues of hand transplantation is still being debated. Allogenic hand transplantation is not life-saving. Life-threatening diseases treated with solid organ transplantation is widely accepted but hand reconstructive transplantation is less widely accepted. Cost of surgery vs prosthesis analysis is crucial considering the huge financial burden due to the lifelong immunosuppression treatment. Hand is defined as an organ and donation laws applies for HT also.[13] As a treatment HT does not require new legislation and is possible within the existing regulations. The complete in-depth risks/benefits must be explained to the full understanding of the patient to take decision on his own. Hand transplantation procedures are exceptionally favourable for both patients and also for the physician. ***From ethical point of view, once the patient has been thoroughly informed of the potential complications following HT ,he or she should have the right to choose a treatment that can improve the quality of life.***[14]

Organisational aspects: A multidisciplinary **transplant team** is formed from a wide range of medical, surgical and supporting specialities. They are grouped into surgical, medical and allied professionals teams and a well-coordinated effort is needed for success of the Transplant program.[15]

Table.2: A hand transplant centre requires a multidisc iplinary team

Physicians/speciality	Health care aid
Replantation surgeon Plastic surgeon Orthopaedic surgeon	Ethics committee
	Psychology
Transplant surgeon	Rehabilitation services Occupational therapists Physiotherapy
Psychiatry	
infectious diseases	Social worker
Immunology/ Haematology	
internal medicine	
Physiatry/ Neurology	
Anaesthesia	

Economic aspects:
Social workers and dedicated transplant financial services representatives coordinate with patients for their insurance and financial needs related to the hand transplant procedure. Insurance companies provide many insurance plans and patients may verify coverage and authorization requirements prior to surgery. Before the proposed transplantation it is essential to bear in mind the costs involved for medications, management of complication, health care-related expenses and other incidentals expenses. International financial services are also available for patients from other countries.[16]

Preoperative workup details:
Patient selection process is initiated by a psychiatrist and transplant social worker. Recipient screening in relation to their anticipations and needs must be completed by psychiatric evaluation before surgery. Social screening helps early selection for the surgery and minimizes psychiatric morbidity following surgery.The pre-transplant evaluation is done by the transplant coordinator for patients prior to wait-listing. Psychiatric assessment must continue in the recovery phase also after transplantation.[17] Donor hand selection for transplant is based on skin color, hand size and muscle bulk. Patient selection must be of same sex and in comparable age groups. The expectations and concerns of the patients must be addressed and documented. There's no guarantee regarding final regain of hand function. With adequate physiotherapy and rehabilitation patients will be able to do basic functions and daily activities:

- They can pick up small objects like nuts
- They can lift jug with full milk using transplanted hand
- They will be able to use spanner and smaller tools
- Make an outstretched palm to receive change
- Make use of knife and fork for eating, will be able to tie shoes and catch a ball.

Patients are sent for medical evaluation, surgical, neurological and orthopedic consultations. Financial counseling, coordination with the family and pharmacy for uninterrupted immuno-therapy are crucial. Psychosocial evaluation and nutrition/dietitian consultation must be done. Hand therapists make assessment in pre-operative and intra-operative periods. The functional needs are assessed and measurements are recorded before surgery by physical therapists and occupational therapists. Therapy team must be informed about the anatomical and surgical details, so that they can plan their therapy program. Infectious disease control and anesthesia consultation are undertaken before the surgery. Extensive and periodical laboratory studies of both donor and recipient includes blood and tissue type are most important for the success of transplant.[18] The routine tests done include:

- Anti-HLA alloantibody (HLA-Ab) screening is done in the preoperative phase
- A panel-reactive antibody test (PRA test) and estimation of percentage of PRA score.
- Cross matching.
- Echocardiogram
- ABO-type of recipient at preliminary evaluation is done and rechecked periodically for ABO antibodies.
- CBC, viral screening and metabolic profile are done during preoperative evaluation.

Imaging studies:
Posteroanterior and lateral view radiographs of both elbow and wrist joints of both upper extremities are taken to compare both donor and recipient limbs. Assessment of structure of donor bones and size of the hand are done preoperatively and should be similar to that of the recipient.[19] Preoperative CT angiography of the **recipient's** affected limb is done to assess the vascularity. Atrophy of proximal musculature, fibrosis or contracture of forearm stump must be studied by MRI of musculoskeletal anatomy. **Electromyography and nerve conduction neuro-physiologic studies** like nerve conduction velocity (NCV) and compound motor action potential (CMAP) testing are done. They are useful for evaluation, progression and monitoring of reinnervation of muscles and their functions post-transplant at follow up visits.

Preoperative immunosuppression must be initiated as per the protocol followed in the centre.[20] Calcineurin inhibitor, tacrolimus (FK506), an antimetabolite, mycophenolate mofetil, a poly-clonal depleting antibody (Thymoglobulin), a monoclonal depleting antibody(Alemtuzumab) or a non-depleting antibody (Basiliximab) and a steroid such as methyl-prednisone are the medicines used during induction phase.[21] Regional axillary nerve block minimizes the post-operative pain. Vasodilatation effect on the peripheral vessels of extremity increases the blood flow to the donor hand. Transplant centre's pharmacy must be equipped with the required basic medicines like antibiotics, antihistamines,

narcotics, analgesics, laxatives, gastrointestinal prophylaxis medications, and aspirin. Anticoagulation low-molecular-weight dextran with heparin may be required for intraoperative and postoperative management. Immunosuppressive medications must be available in sufficient stocks for the patient.

CHIMERISM:

Chimera carries two distinct sets of DNA, each with a genetic code to make a completely separate person. Donor and recipient immune cells coexist in a chimeric immune system and induces tolerance and limits rejection rates. ***Chimerism makes adapt the immune system to tolerate the coexistence of donor and recipient immune cells.***[22] Post-transplant goal is creation of a state of chimerism to decrease postoperative immunosuppression drug dosage. During induction therapy, the recipient receives infusions of bone marrow cells from the donor to develop tolerance of donor antigens. Alloreactive leukocytes can be eliminated by injection of donor pluripotent haematopoietic stem cells that reprograms recipient immune system. Presence of circulating donor lymphocytes as low as 1% induces sufficient tolerance. There is reduction in the dose of immunosuppressive drugs required and enhances the success rate of the procedure. Induction with alemtuzumab and tacrolimus maintenance after transplant is being followed without any graft loss.[23,24]

Rejection and immunosuppression therapy: Increased concentration of local immune cells and tissue specific antigens make skin the most antigenic. The relative antigenicity of tissues is skin > muscle > bone > cartilage > nerve. Rejection episodes to composite tissue allotransplantation (CTA) in recipients are mediated by immune mechanisms that are similar to solid organs rejection episodes.[25] ***Rejection episodes are monitored by regular skin biopsies in postoperative period during follow-up visits***. Histological classification of CTA rejection: (Schneeberger et al and Cendales et al.)[26]

- Initial presentation involves perivascular infiltrate progressing to the dermis.
- Arteritis of medium to large arteries of subcutis associated with myositis is the next stage.
- Advanced stages of rejection show perineural involvement without frank neuritis.
- Predominance of CD4+ in milder cases and CD8+ in advanced cases in the infiltrate is the characteristic feature.

Immunosuppression therapy aims at prevention of graft rejection and avoiding immunity related complications like sepsis, end-organ damage, and neoplasia. Medications are used during the induction and maintenance phases following transplantation.[27] For the ***induction phase***, tacrolimus (FK506), myco-phenolate mofetil (MMF), Thymoglobulin, alemtuzumab, or basiliximab and methyl prednisone are used. ***Maintenance medications*** commonly used are steroids, anti-metabolites and calcineurin inhibitors. They are used in much lower doses than during induction phase. Induction with campath is being used recently, followed by a steroid-free regimen. Other organ transplantation surgeries have also shown promising results with steroid-free maintenance therapy.[28]

Protocols and dose schedule in CTA vary among centres around the world in choice of agents for induction (anti-thrombocyte globulin [ATG], basiliximab, Campath-1H) and number of drugs and dosages in maintenance drugs. conventionally in solid organ transplants triple drug combination therapy(FK506+MMF+steroids)is used. Tacrolimus monotherapy after depleting antibody induction and followed by steroid avoidance protocols has been used successfully.

Table.3: Immunosuppressive protocol in Lyon, France

Induction Therapy	Maintenance Therapy	Dosage/Blood level
Prednisolone	Prednisolone	5 mg/d
Tacrolimus	Tacrolimus	5 and 10 ng/ml
Mycophenolate Mofetil	Mycophenolate Mofetil	2g/d
Anti-thymocyte globulins	-	10 to 30 mg/kg IV qDay

Induction therapy for transplant patients aims at reduction in initial acute immune responses. Preparing patients require depletion of T-and B-cell stores with several cycles of ***induction therapy.***[29] They are associated with an interference in adaptive immune response on allo-antigen presentation with transplantation. Recently, polyclonal or monoclonal antibodies against thymocytes like thymoglobulin and alemtuzumab are used as induction agents and there is no need for long-term steroid use. Hence the cardiovascular risk factors and complications associated with long term steroid use are avoided. **Maintenance therapy** is initiated when transplantation is done. Triple-drug therapy regimen is commonly used in many centres. (1) Tacrolimus, a calcineurin inhibitor prevents early activation of T cells;(2) mycophenolate mofetil, an antimetabolite agent prevents synthesis of nucleotides required in lymphocyte proliferation and (3) Prednisone, a steroid are used in combination.

Donor limb retrieval is done under strict sterile condition in an operating suite. An above-elbow tourniquet is placed and disarticulation at elbow is performed. The tourniquet is left in place, perfect haemostasis is achieved and the wound is closed. This prevents the blood loss during the retrieval process. Skin staples helps reduce the closure time of the wound.[30] A cannula is passed immediately into the artery of retrieved limb and irrigation with *University of Wisconsin solution* chilled at 4°C is done. The solution consists of potassium lactobionate, KH_2PO_4 and $MgSO_4$. The other constituents of the solution includes raffinose, adenosine, glutathione, allopurinol and hydroxyethyl starch. The solution increases duration of allowable ischemia. The limb is covered with a moist gauze, put in to a box and stored at the cooler. Preparation for transport of the limb to the recipient hospital is already completed and a rapid transport system is available. Irrigation is continued while limb is being transported. A life-like limb prosthesis must be arranged before donor limb retrieval. After death of the donor the prosthesis must be fit in place of the donor limb if open casket ceremony is planned.

When a donor becomes available a ***rapid transport*** system must be arranged to avoid delays to transport the recipient to the transplantation centre.[31] Screening tests for the donor limb need to be completed before transplantation. Recipient must undergo repeat of complete blood count, assessment of coagulation and metabolic profiles, and ABO antibody screening **just prior to the surgery.**

At the recipient hospital, the donor arm is received, unpacked from the cooler and arranged for dissection on a surgery table. For unilateral hand transplant, operating room set-up must preferably be in the same room. Operative teams work on the recipient and donor limbs preferably in the same operating room for better communication between the 2 teams. Chilled Ringer lactate solution is used to flush out the University of Wisconsin solution. Upper extremities and both legs of recipient should be shaved and kept ready, for a possible tendon graft harvest. The main hand transplant surgeon operates on the recipient limb. Dissection of donor limb is done by the assistant hand transplant surgeon. One scrub nurse per extremity, two circulators per room and an anesthesiologist assist the surgical teams. For bilateral hand transplantation procedure more personnel and equipment are needed as required.

Transplantation surgical details are similar to hand replantation. Once retrieval of donor limb is completed and mode of transport are already arranged, recipient stump preparation can be started. Should there be any concern regarding quality of allograft retrieved, delay recipient preparation for surgery till the donor limb reaches the centre. Donor limb quality must ascertained on arrival and then surgery should be started.

Preparation of the donor limb:

- University of Wisconsin solution is flushed out with Ringers Lactate solution
- Skin and bone in excess of the expected must be removed.
- Identify all tendons, arteries, veins, and nerves and tag with sutures.
- Measurements made at initial evaluation are checked and radius and ulna bones are shortened as planned.

The recipient limb dissection is commenced to identify vital structures such as the arteries and veins, nerves, and tendons. Skeletal fixation and stabilisation are achieved with plate and screw fixation of ulna and radius bones after are done fashioning to match the donor bones. The tendons are repaired using the standard techniques. The nerves, arteries and veins are repaired under microscopic magnification. If the recipient tendons are found to be atrophic, tendon transfer procedures or mass repair of recipient and donor hand tendons may be necessary. For deficiency of tendons, graft from the opposite extremity or from the lower extremity are harvested and used. Wound coverage can be achieved by use of skin grafts. A long-arm splint is given for the hand and arm at the end of the procedure and maintained during the immediate postoperative period and replaced with proper dynamic splint later on.

The Basic surgical techniques are similar to reimplantation procedure.[32] One team is involved in harvest of donor limb and other team prepares recipient limb. Ideally both are performed in adjacent operating rooms for better communication and coordination. Tendons and muscles in the forearm, nerves, arteries and veins of both donor and recipient limbs are identified and tagged for comfort of repair. The radial and ulnar artery and veins accompanying the arteries are also dissected. Anastomosis of veins involves multiple peripheral veins of fairly larger size. At the level of middle forearm, multiple veins on the dorsal and ventral aspects are identified in both recipient and donor limbs. Major nerves of the upper extremity namely radial, ulnar, and median must be identified and kept ready for repair.

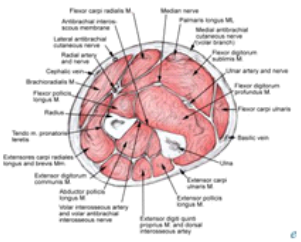

Fig.1: Structures to be repaired during hand transplan tation procedure: cross-sectional anatomy of the forearm.

Rigid fixation of forearm bones of the recipient and donor by plate-and-screws is done for stability at the beginning of transplantation surgery. If the recipient tendons are found to be atrophied, it should be sutured to the entire group of flexor or extensor tendons of the donor. Operative sequence of replantation procedure is followed for transplantation surgery also.(1) For proximal level replantation involving large muscle mass, a vascular shunt is made first. This will the minimize warm ischemia time and help better survival of the limb. (2) After adequate irrigation, through debridement of soft-tissues is done. Rigid bone fixation with or without shortening is carried out as planned with imaging studies. (3) extensor tendons are repaired (4) repair of arteries is done. if ischemic time is >3-4 hours repair artery as second step immediately after bone fixation(5) anastomosis of multiple veins (6) repair of flexor tendons (7) repair of all major nerves and (8) wound closure with or without fasciotomy.

Azari's theory is the method of preparing hand for transplant during the initial amputation surgery itself. Other patients waiting for a hand transplant, had undergone typical amputation surgeries previously. In Azari method, the hand amputation is done and at the same time few steps are carried out in preparation for a hand transplant.[33] The hand was amputated closer to the wrist than the elbow. This step retains the length of all the nerves and tendons. The divided structures were sutured together. To prevent retraction of tissues they were attached to the stump of bone. This makes sure plenty of tissues available for surgery at a later date. The transplant procedure to replace the lost hand was performed by the team headed by Kodi Azari on October 26, 2016 that lasted for about 17 hours. They demonstrated movement of patients thumb just after two hours after recovery and he was able to move his entire hand in only two days following surgery.

Postoperative Monitoring should be continuous in a specialized post-operative care unit. The nursing staff monitor status of blood circulation to the transplanted limb and its viability is assessed continuously every hour. Pulse oximeter help monitor blood flow to the transplant hand and is compared with patient's normal limb. Surface skin temperature of transplanted hand is compared with the temperature readings of unaffected extremity. The normal value of surface skin temperature should be at least 30°C. The postoperative care physician should be immediately informed if skin temperature is reduced or alterations in circulatory status of the limb. Ambient room temperature should be maintained at 75°F (24°C). Complications in the postoperative period include, neuroma formation, progress of callus formation, heterotopic ossifications and scarring in the post-operative period. These complications can be detected and their progression can be assessed by plain radiographic studies and other imaging studies such as high resolution ultrasound (HRUS), CT, and MRI. Development of AV-fistulas with a risk of hypoperfusion of the limb must be readily detected and monitored. Muscle and tendon function can be studied with the help of dynamic ultrasound.

Postoperative immunosuppressive medication regimen is crucial for success of transplant program. Transplant coordinator ensures uninterrupted availability of medications and administration is monitored by transplant physician. Periodic estimation of drug levels in blood should be done and documented.[34,35] Screening for development of anti-donor antibodies in post-transplant blood samples must be done at regular intervals. Skin biopsy findings along with serum testing are useful for correlation of histology with systemic markers of immunologic activation. Skin biopsy studies are done at regular intervals and also whenever there is suspicion of rejection or presence of infection. In post-transplant period general hematologic and chemical studies must be done periodically. Microbiological support and facilities for rapid therapeutic drug level estimation are also important.

Adequate control of pain, nutrition management, monitoring activity level, bowel and bladder care are essential components of post-operative management. Anti-embolic measures must be assessed by nursing staff. ***Physical and occupational therapy*** is done daily starting from first post-operative week. The exercise guidelines are based on tendon repair techniques of 4-6 strands. Tendon gliding is greatly enhanced by muscle stimulation with electrical stimulation. Electrodes are placed along the median and ulnar nerves, with a transcutaneous electrical nerve stimulator.[36] Both static

and dynamic splinting are useful in rehabilitation following hand transplantation. Most useful splint for mobilization has the design of proximal inter-phalangeal crane outrigger and cast outrigger with incorporation of static metacarpop halangeal flexion and with dynamic thumb interphalangeal extension. The crane outrigger blocks metacarpal joints in flexion and at the same time allows active flexion and has dynamic interphalangeal extension has advantages of good healing, gentle range of motion is possible, and prevents adhesion formation. After 3 weeks, an anti-claw splint for the hand can be used with the outrigger.[37] Edema management measures including compression gloves must be followed.

Things to be strictly avoided: caffeine and smoking have vasoconstrictive effects on the blood vessels and they must be strictly avoided. Family members and friends must avoid smoking before visiting the patient.

Transplant coordinator educates patients and their family on medications and restrictions in activities. They monitor and make necessary changes in activities related to daily living for healing and recovery of the transplanted limb. Patients get adapted to the "new" hands of their own by seeing and using the new hand. Issues related to body image and identity must be addressed following transplant. Compliance with health care needs of patients in the pre-operative period helps to modify postoperative psychotherapy requirements by the social worker and psychiatrist. Always ensure positive but realistic expectations, especially in relatively young age of CTA transplantation. Patients with hand transplant may develop postoperative emotional reaction, may have adverse effects on the program and rehabilitation of the patient. Priority is given for prevention and treatment of such adverse reactions. Psychiatric counselling before surgery will help reduce the stress or anxiety related to the procedure and recovery. Psychiatric counselling is continued in the postoperative period and concerns related to the new limb must be discussed and minimized based on individual results.[38,39]

Early postoperative complications include vascular thrombosis, deep venous thrombosis, limb loss and bleeding. Infections involving surgical wound and risk of pneumonia are common. Incidence of cytomegalovirus (CMV) infections are increased. Prolonged surgical procedure and immunosuppressive therapy related complications are most important. Risks of thrombus formation are less with experienced microsurgical team. Vascular re-exploration and revision of venous anastomosis with either end-to-end or end-to-side techniques can salvage the transplant. Edema in the postoperative phase is identified with volumetric analysis of limb and can be managed conservatively by elevation and compressive bandaging. Venograms or lymphangiograms help exclude venous stasis or lymphedema. Variety of tissues components in VCA have differing antigenicities and poses a great challenge to avoid rejection. Skin has extremely antigenic tendency and requires an aggressive immunosuppression. **Neuromas and regional pain syndrome:** Nerve repairs of upper extremity are complicated and may result in neuroma formation and may result in regional pain syndrome.

Transplant rejection: The recipient's immune system rejects the transplanted tissues of a donor hand and destroys the transplanted tissues.[40]

- **Hyper-acute** rejection is due to presence of completely unmatched antigens. It occurs within few minutes after the transplant procedure.
- **Accelerated rejection** is mediated by non–complement-fixing antibodies to antigens present in donor tissues, occurs on the third to the fifth day following transplantation. Elevated systemic temperature associated with swelling of graft, reduced urine output and tenderness are characteristic features.
- **Acute rejection** begins as early as 1 week following transplantation, with highest risk in the first 3 months. It can happen months to years later also. Donor hand produces antibodies and immune system targets to destroy blood vessels and tissues in donor hand. Features associated with acute rejection are rash formation, swelling and color changes in the skin of the transplanted hand or arm. They may be associated with or without pain and are usually controlled with medications. Repeated rejection episodes may lead to chronic rejection. The donor transplanted hand or hands will have to be removed at rare instances of failure to control rejection episodes. Previous acute rejection is not a disqualification for another hand transplant, but match with a donor becomes more difficult.
- **Chronic rejection** happens over longer period of time. Clinical features include changes in the hair and nails in transplanted hand. Hair loss on hand and changes in the finger nails are noticed. The hand may lose function and become painful. Confirmation is done by tissue biopsy and dosage of anti-rejection drugs need to be increased.[41]

Complications due to immunosuppressive therapy: To avoid rejection of various tissues such as foreign skin, muscle, nerve, bone and tendon in VCA is the most challenging aspect of hand transplantation. Skin has an extremely antigenic tendency and requires more aggressive immunosuppression for the rest of life following a hand transplant. About 90% of patients have metabolic complications like hyper-glycemia with increased incidence of diabetes and end-stage renal disease, Cushing syndrome and hyperparathyroidism. Transplant-related complications include clinical entity called post-transplant lympho-proliferative disorders and increased incidence of basal cell carcinoma of the nose. There is risk of increased cholesterol level, incidence of heart disease and hypertension.[42] Opportunistic infections with serious infections, including cytomegalovirus is seen in approximately 77% of patients at some point during follow-up.[43] They suffer from serum sickness, increased susceptibility to bacterial, chronic viral and fungal infections. Less common complications include avascular necrosis of the hip, acne formation, headaches, nausea, weight gain, sleeplessness, diarrhea, hair loss and bruising. They may be associated with nephrotoxicity, neurotoxicity, gastrointestinal toxicity. Osteoporosis is common and osteo-necrosis of the hip has an incidence of 5%. Look for asymptomatic osteo-necrosis of hip with MRI study of both hips early within a year and recheck annually following transplant. Steroid-related complications are mostly transient or reversible. Minimizing the dose of bolus steroids for treatment of rejection or following steroid-free protocols will reduce their complications. Hand transplantation patients on steroid-free immunosuppression regimes have never reported to suffer from graft versus host disease and chronic rejection episodes. There has been no incidence of malignancies or life-threatening conditions in this group of patients. American and European studies have higher survival and success rates of hand transplants compared with other forms of solid organ transplants. Meticulous psychosocial screening and follow-up for psychological considerations and body image disorders are important.

Management of acute rejection episode: Skin changes due to acute rejections in CTA must be confirmed by biopsy findings and are diagnosed earlier than solid organs rejection reactions. The typical rejection episode is appearance of maculopapular patchy rash with or without swelling of the hand. The rejection episodes can be managed by increasing the dose of immunosuppressive agents temporarily, by administration of bolus doses of steroids along with topical immunosuppressive and steroidal creams. It is relatively simple and successful to manage acute rejection and intermittent episodes of acute rejection following

transplantation. It is crucial to follow safety measures in spite of good success rates of hand transplantation and the availability of proper immunosuppression.[44] In case of failure an exit strategy is amputation of the rejected hand and prosthesis can be advised. The rejection is not a contraindication for another hand transplant.

Prolonged use of steroids is responsible for nearly 50% cardio-vascular side effects and complications due to infections in patients related to transplant loss. Long-term use of Tacrolimus results in complications such as nephrotoxicity, diabetes, hypertension, infection, and neoplasia. Newer protocols avoid or minimize the doses of steroids and use Sirolimus instead of tacrolimus. Tacrolimus has the advantage that it facilitates nerve regeneration with primary repair as well as nerve grafts are used.[45]

Currently various steroid minimization or avoidance protocols of immunosuppression are being used. Calcineurin inhibitor sparing protocols have switched to mTOR inhibitors for long term treatment. Maintenance regimens include mTOR or mycophenolate mofetil-based drugs. Recently, Alemtuzumab is being used for induction therapy. Newer protocols use cell-based immuno-modulatory drugs and then are followed by long-term immunosuppression minimization or weaning schedules. Good responses are achieved with non-myeloablative induction strategies and biologic agents (Belatacept is a T cell co-stimulatory blockers) are also used in combination with other immunosuppressants.

Follow-up: The patient needs close monitoring for 12 weeks following hand transplant surgery. It is ideal the patient lives nearby after discharge from hospital for any eventuality. Weekly assessment of laboratory values and clinical status is essential for several months. The transplant coordinator is always available to respond to the issues related to transplant and patient's concerns. Any suspicious changes in clinical or laboratory finding must be reported to the treating physician. After 12-week postoperative follow up period, the patient needs assessment at periodic intervals at 3 months and 6 months, 1 year, and then annually. The transplant coordinator should arrange for the follow up care of the patient and monitor compliance of patient regarding the intake of the medications.

Hand transplant recipient's transition to home is the responsibility of hand transplant co-ordinator, takes care of all aspects of patient's needs, plans and makes necessary arrangement. A ***mirror team*** consisting of an internist and hand physical therapist is ideal for follow up of patients near their homes. If a hand surgeon specialist is available in patient's home town he should be made part of the team. If a hand surgeon is not available, another surgeon is involved to get biopsy specimens and to monitor the patient's care. Original transplantation team is responsible for management of transplant-related illnesses. Patient's primary care physician must be entrusted to management of coexisting medical conditions, such as hypertension and diabetes. Hand transplant rehabilitation protocol consists of four phases according to Brigham and Women's Hospital (BWH) Hand Transplantation Team:

1. Preoperative phase consists of through functional assessment, establish goals and expectations of the patients and ensure compliance of patient for immunotherapy and possible complications of transplantation and immunotherapy.
2. Initial postoperative (weeks 1–2): Hand protection, achieve good healing, minimize swelling of hand and edema reduction protocols. This phase includes patient and family education, and the process of discharge.
3. Intermediate (weeks 2–8): Aims at prevention and/or decrease scar adhesion; Therapy to be continued for scar management; Goal of therapy is to increase tensile strength and flexibility. Achievement of full range of function and prevention contractures of all joints is the priority.
4. Late (from 8 weeks and after): Full functional status must be achieved with normal strength; every effort should be made for transition to routine activities.

Therapist will administer quantitative tests of upper limb function during follow-up visits. The common measures of function performed in the rehabilitation phase include Carroll upper extremity function test, 400-point test, activities of daily living and quality of life evaluation (RAND-36). ***Carroll test*** is to assess patient's ability to perform activities of daily life that involve the upper limbs. It remains the standard test for hand transplant recipients. Evaluation of functional capacity of transplanted hands is best done with disabilities of the arm, shoulder, and hand (DASH score).[46] Functional score system to analyse functional results has been formed by the International Hand Registry. The Hand Transplantation Score System (HTSS) is based on many criteria. A total of 100 aspects are evaluated. The most important aspects of the assessment include appearance, sensibility and movement. Work status and daily activities are best indicators. Psychological and social acceptance, patient satisfaction and measures of general well-being are other important components of this system. There is an appreciable improvement for the first 3 years, and then tend to become stable.

Second-stage corrective surgery after the initial transplant surgery, if required may be performed between 8 and 12 months of transplantation. Clinical and radiological evidence of bone healing is indication for removal of the internal fixation device. The flexor and extensor tendons may require procedures to release adhesions. Other secondary procedures include arthrodesis of the left first metacarp ophalangeal joint; myo-tenolysis of wrist and flexors of fingers.

An Ideal hand VCA unit should be planned in an academic centre with an existing solid organ transplant unit. The ethicist sorts out ethical implications related to Hand transplant. Success of hand VCA unit needs dedicated coordination, adequate funding, dedicated health care team and patient compliance. Hospital administration should ensure open communication and coordination of all transplant-related services and multiple disciplines involved. Transplant surgical team includes hand transplant surgeon, orthopaedic and plastic surgeons. Peri-operative coordination with specialities like immunology, internal medicine, psychiatry, infectious diseases, haematology, dermatology, neurology, anaesthesia and physiatry must be ensured. As immunosuppressive drugs are expensive and lifelong therapy is required, drug coverage commitment by the institution regarding uninterrupted supply is essential. Occupational and physiotherapist's role in the post-operative rehabilitation is important for success of Hand transplant program. Continuous psychological and social support is crucial throughout the transplant process for both patients and family as this surgery carries great psychosocial impact.[47]

Outcome and Prognosis: Hand transplant recipients are young healthy individuals with normal life expectancy whereas most solid organ transplantation are done in elderly patients with comorbidities. Solid organs transplantation has chronic rejection that can occur nearly a decade after the procedure. Long term and large series need to be analysed to know hand transplantation will also meet with a similar fate as solid organ transplantation. Healthy individuals likely to outlive transplanted limb may have potential dilemma regarding the procedure with all the risks of surgery and drug related complications. In case of rejection that cannot salvage the limb, amputation is done without serious consequences. The longest surviving transplanted hand of 20 years remains

free of any evidence of chronic rejection.[48] Lack of chronic rejection in hand transplantation is due to presence of bone marrow that is responsible for development of higher partial tolerance.

Peripheral nerve regeneration and cortical reintegration are important to achieve a functional result. Transplanted hands have recovery of sensibility and motor function that ranges from satisfactory to excellent result categories. Sensation achieved as measured by return of 2 point discrimination is seen in majority of cases and all patients develop protective sensation.[49] Reorganization occurs in corresponding homunculus and it has been confirmed by functional MRIs of brain that it recognizes transplanted new hand. Acceptance of the new hands as their own in most patients has been demonstrated by their improved manual skills and return to work. Improvement of body image and overall quality of life has been documented in recipients. Patient compliance with strict adherence to immunosuppression on a regular basis ensures better outcome of graft survival in hand transplan tation and superior than solid organ transplan tations. It is noted that complications like chronic rejection episodes and late loss of allograft are also less compared to solid organs. (Breidenbach, et al 2016)

Transplantation procedures involving above-elbow arm level is relatively simpler compared with distal forearm or wrist transplantations techniques. Micro-surgical expertise is not required as the vessels above elbow are larger in size. The arm contains vascularized bone marrow transplanted and that induces chimerism and promotes tolerance.

Disadvantages:
Reinnervation of forearm muscles is crucial for final functional outcome. When the distance and duration of nerve regeneration and reinnervation is prolonged, the intrinsic muscles of the hand are not fully functional and the final outcome may be compromised in above-elbow arm transplantation. Presence of vascularized bone marrow makes recipient more susceptible to graft-versus-host disease.[50]

Paediatric and congenital Hand transplantation: The first heterologous paediatric hand–forearm transplant in a child was performed in 2015 in the United States and has proved the surgical feasibility. Paediatric recipients have good functional outcomes with gain in cortical somato-sensory reintegration. A four drug immunosuppressive regimen was used to control rejection for first paediatric hand–forearm transplant patient. Advances in immunotolerance techniques have helped expand the application of VCA in children. Paediatric VCA patients who have most potential gain are bilateral upper extremity amputees. The critical factor is their ability to engage in the rigorous demands of rehabilitation. Transplanted limbs continue to grow till the bony growth plates remain intact. Reconstruction of joints, preservation of epiphyses, and minimizing bone shortening as much as possible are crucial in child hand transplants. It is important to remember that there is a complementary growth of both donor and recipient extremities.

Proper size matching of donor and recipient limbs is particularly challenging in children, due to age-related variability. Computed tomography imaging studies and 3-dimensional printer technology are used for donor hand transplantation in children. Recipient forearm anatomical models are made in three-dimensions with materialise Mimics (Materialise interactive Medical Image Control System), with volumetric scaling applied for getting spatial alignment of bony landmarks.[51]

Another challenge in paediatric patient is maintenance of adequate hemodynamics. They require approximately 60 ml/kg of washed, irradiated, CMV sero-negetive and leuko-reduced packed red bloods cells and fresh frozen plasma during the surgery.[52] Administration of steroids may impact growth and the health of the bone. Potential complications and the longevity of life of the child must be considered during child selection for hand transplant. Ideally children above the age of 8 may be able to fit into the rigorous rehabilitation programs.

Reconstruction of metacarpal hand with multi-digit allotransplantation: Metacarpal hand is a result of amputation of all fingers and functionally considered equivalent to hand amputa-tion. (Rampazzo et al 2015) Multi-digit allotransplantation involves transfer of 4 fingers and thumb as a single allograft based on both radial and ulnar arteries. Dorsal digital veins are dissected till the confluence of major veins. Division of common digital nerves are done at their origin. The flexor and extensor tendons are divided in zones V and VI respectively. Disarticulation of fingers are done at MCP joint level. In experimental mock transplantation procedure, ulnar and radial arteries were injected with red and blue India ink. Later ulnar artery was injected with lead gel and perfusion of the fingers was studied. Index finger remained a water-shed area as confirmed with digital radiographs and computed tomographic scans. Well-designed clinical studies are required to validate these feasibility studies.

Controversies and Future:
Hand transplantation procedure is for improvement of quality of life and not considered a life-saving procedure. The decision has to be taken on patient's own will keeping in mind all the complications and cost involved. First bilateral above-elbow transplant in Munich and subsequent procedures had positive outcome but still has been debated. Cellular therapeutic strategies including allogeneic stem cell transplantation to induce tolerance are recent concepts under research. Steroid-free and less toxic immuno-suppressive drugs protocols along with newer strategies will significantly impact success of hand transplantations in future. It is likely to redefine composite tissue allotransplantation based reconstructive surgery. In recent future, hand transplantation and prosthetic technology will improve at a greater pace. Developments in prosthetic technology are interesting and promising and they are likely to significantly impact the indications for hand transplantation.

1) Immunotolerance has been reported in animal models. Research is on to find methods of induction of donor-specific tolerance and sensitization. Efforts are on finding more sensitive monitoring strategies of rejection. Indication for hand transplantation will increase with availability of induction of donor-specific tolerance. Safe transfer or vascularized composite tissues can be achieved with risk of chronic rejection episodes are reduced or even eliminated. This may result in much improved motor and sensory outcomes.
2) Design of prosthetics is rapidly developing and expanding. Prosthetic control algorithms technologies include pattern-recognition. Tactile and proprioceptive feedback technologies also help design complex mechatronic devices that will function as well as have control.
3) Implantable sensors transmit myoelectric signals to the prosthetic device. Thus man-machine interface can be enhanced.
4) Recent research on different muscle and also direct nerve interfaces have reached their first clinical applications.[53,54,55]

CONCLUSION:
Hand transplantation has evolved into a surgical marvel since first hand trans-plantation was attempted. With recent advances in study of immunology and availability of newer immunosuppression drugs, prevention of allograft rejection and achieving good functional recovery is made possible

with hand transplantation. The cost of the procedure and the need for a lifelong potentially harmful medication prevent it being a justification for indication. This will have a direct negative effect on an already strained healthcare system. Immune tolerance can be achieved in near future with the availability of newer technologies. By current research, the costs of the procedure and medication-related potential side-effects of post-transplant therapy can be reduced. Hand transplantation is likely to transform from an experimental procedure to standard practice, as with solid organ transplantation.

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