World Experience After More Than a Decade of Clinical Hand Transplantation: Update on the Innsbruck Program

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• Hand transplantation • Composite tissue • Rejection
• Immunosuppression • Outcome • Psychological aspects

Composite tissue allotransplantation (CTA) is a valid therapeutic option for complex tissue defects in patients in whom conventional reconstructive surgery is insufficient to achieve satisfactory results.[1–10] Candidates for CTA are patients who have suffered massive or complex loss of tissue with prosthesis being either unavailable or insufficient to restore body integrity and function. In such cases, reconstructive transplantation holds the potential of restoring range of motion in

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combination with sensation, resulting in independence and social integration in everyday life.

Between March 2000 and May 2006, 3 patients underwent bilateral hand or forearm transplantation at the Innsbruck Medical University Hospital. Because satisfactory functional outcomes were achieved in these cases and encouraging results with unilateral hand transplantation had been described by others,[7,11,12] unilateral hand amputation was accepted as an indication for transplantation and a first case was performed in July 2009. Widening the spectrum of indication was also influenced by the introduction of moderate-dose to low-dose immunosuppressive protocols. With a total of 7 hands/forearms transplanted, Innsbruck University Hospital represents one of the largest hand transplant centers.

This article reviews the clinical courses of the 3 bilateral hand transplant recipients at our institution, with emphasis on function, immunosuppression, rejection, complications, and graft vascular changes. Bilateral versus unilateral hand amputation as an indication for transplantation is discussed, as well as psychological aspects in hand transplantation.

THE INNSBRUCK HAND TRANSPLANT PROGRAM

Bilateral Cases

Between 2000 and 2006, 3 male patients (23–47 years old) underwent bilateral hand (n = 2) or forearm (n = 1) transplantation at the Innsbruck Medical University Hospital. Comprehensive descriptions of patients and donor selection were published earlier.[2,6,13–16] The first patient was a 47-year-old policeman who had lost his hands when he attempted to deactivate a bomb in 1994. He received a bilateral hand transplant at the level of the wrists in March 2000. In February 2003, the second patient, a 41-year-old electrical engineer, who lost his hands and two-thirds of his forearms in an electrical accident, received a bilateral forearm transplantation. The third bilateral case was performed at the level of the midforearm in a 23-year-old student from the Ukraine in May 2006. He had lost both hands in a bomb blast in 2000. The first 2 patients had been equipped with myoelectrical prothesis before transplantation, and the third patient refused prostheses.

During this period, only bilateral amputation was accepted as an indication for hand transplantation at our center. Restoration of hand function including sensitivity, allowing patients to regain independence in everyday live, was considered as the major goal.

Establishment of the Working Group Reconstructive Transplantation Innsbruck and Establishment of Unilateral Hand Transplantation

In unilateral hand transplantation, patient selection is more challenging because much of the functional deficit is compensated by the remaining hand and a prosthesis. However, the patients' functional needs and psychological impairment differ between individuals. To evaluate the necessity for unilateral hand transplantation in selected cases with significant psychological impairment caused by distal unilateral traumatic amputation, close interdisciplinary evaluation had been suggested.

To meet these aims, a working group called Reconstructive Transplantation Innsbruck (RTi) was founded by members of the Department of Visceral, Transplant and Thoracic Surgery, Department of Plastic Surgery, Department of Traumatology, and Department of Medical Psychology at the Innsbruck Medical University in November 2008. Guidelines for patient selection in bilateral and, in particular, unilateral transplantation have been developed based on surgical, immunologic, and psychological parameters. As a consequence, a 4-step candidate selection algorithm has been introduced and includes basic hand surgical, immunologic, psychological screening (step 1); advanced psychological evaluation (step 2); advanced hand surgical/immunologic diagnostics (step 3); helping to find an interdisciplinary consensus (step 4).

Recommendations have been developed for donor selection, surgical procedures, immunosuppression (IS) protocols, postoperative hand therapy, as well as psychological supportive therapy and detailed psychological follow-up testing including a preliminary suitability score for unilateral and bilateral transplantation.

Applying this novel selection algorithm, the first unilateral case was performed in July 2009 in a 54-year-old man, who lost his right hand in a woodworking accident in 2004. The unilateral hand transplantation was performed at the level of the very distal forearm. Inclusion criteria included significant psychological impairment following step 2 evaluation and loss of quality of life (manuscript in preparation).

PSYCHOLOGICAL ASPECTS IN HAND TRANSPLANT RECIPIENTS

One of the main psychological and psychosocial gains with hand transplantation is the improvement of quality of life, including the improvement

of body image, after loss of 1 or both hands. A psychological assessment of potential hand transplant candidates includes evaluation of quality of life and describes psychological resources and coping strategies for the postoperative period.[17–20]

Motivation for Hand Transplantation

The motives driving patients to seek hand transplantation are diverse and depend on many factors such as functional impairment, lack of sensation, social integration, and the patients' overall physical or psychological status. In general, patients suffering from loss of 1 hand primarily report difficulties with coping and psychological burden, whereas patients with a bilateral loss particularly suffer from the functional impairment and loss of quality of life.

Body image has increasingly been functionalized and standardized by our society. Deviations from the ideal body image are often associated with self-esteem deficits. Body image is not only constituted by body shape, but it also depends on an individual's imagination of the body and the sum of body-related experiences and manifests itself mostly during puberty. Subsequently, body image is primarily influenced by social norms. Because body shape has gained increasing attention in the present, appearance-oriented society, it plays an important role in social integration and self-esteem.

As a consequence, it is increasingly difficult to live with physical deficits, to cope with the related psychological distress, and to compensate for the disadvantage in social integration. Reconstructive transplantation represents a novel method that allows for reconstitution of not only function but also body integrity. Therefore, the evaluation of emotional aspects represents an essential parameter in the psychological assessment of potential candidates for unilateral /bilateral hand transplantation.

Psychological Evaluation of Candidates for Reconstructive Hand Transplantation in Innsbruck

In the last decade, 4 candidates passed the clinical psychological assessment for bilateral or unilateral hand/forearm transplantation at our institution. All 4 candidates showed multiple, but minor, psychological irregularities as well as a reduced quality of life following hand/forearm amputation. Two candidates were declined because of psychiatric contraindications. Specifically, the required psychological resources and copying strategies were lacking.

Before transplantation, the strongest motivational aspect in the 3 bilateral hand or forearm transplant recipients was the expected improvement in function and quality of life. Concerns were primarily related to personal economic development. The primary motive in the patient suffering from unilateral hand amputation was his psychosocial well-being and the associated quality of life. Issues such as social withdrawal, embarrassment, reduced self-esteem, and a depressive coping style represented the essential elements in the psychological assessment of this patient.

To assess potential candidates for unilateral/bilateral reconstructive hand transplantation, a standardized Psychological Screening Program for Reconstructive Transplantation (iRT-PSP) was introduced recently. It consists of a detailed psychological interview that covers central issues related to reconstructive transplantation (eg, motivational aspects, coping skills, general compliance, concept of body and self, quality of life) and uses the following psychometric instruments for screening procedures and follow-up ratings: (1) Response Evaluation Measure (REM-71; a survey to evaluate an individual's defense mechanisms[21]), (2) Brief Symptom Inventory (BSI; a general evaluation of psychiatric symptoms[22,23]), (3) Essener Coping Questionnaire (a German questionnaire to measure disease-associated coping skills[24]), (4) Life Orientation Test-Revised (LOT-R; a test to assess individual differences in generalized optimism vs pessimism[25,26]), (5) Medication Experience Scale for Immunosuppressants (a German scale to evaluate compliance, focusing on immunosuppressants[27]), (6) Multidimensional Body-Self Relations Questionnaire (MBSRQ; a questionnaire to measure body image and organ fantasies[28,29]), (7) SF-36 Health Survey (a survey to measure quality of life[30,31]), and (8) the Transplant Effect Scale (TxEQ; a scale to measure potential post-transplant effects[32,33]) (**Table 1**).

We believe that pretransplant psychological assessment and posttransplant psychological counseling is essential for critical evaluation of the suitability of potential transplant candidates and may help to minimize the psychological morbidity of hand transplant recipients.[34–36]

Psychological Considerations and the Unilateral versus Bilateral Hand Transplantation Debate

Because restoration of function was considered to be the main goal, only bilateral amputees were accepted as candidates for hand or forearm

Table 1
Psychometric instruments of the Innsbruck Psychological Screening Program for Reconstructive Transplantation (iRT-PSP) and appendant constructs

REM-71 by Steiner et al[21]; German version Abwehrfragebogen by Schüßler et al (manuscript in preparation)	Survey to evaluate an individual's defense mechanisms
BSI by Derogatis et al[22]; German version by Franke[23]	General evaluation of psychiatric symptoms
Essener Coping Questionnaire (Essener Fragebogen zur Krankheitsverarbeitung) by Franke et al[24], (adapted for unilateral/bilateral hand transplantation)	German Questionnaire to measure disease-associated coping skills
LOT-R by Scheier et al[25]; German version by Glaesmern et al[26]	Test to assess individual differences in generalized optimism vs pessimism
Medication Experience Scale for Immunosuppressants (Medikamenten Skala für Immunsuppressiva) by Goetzmann et al[27]	German scale to evaluate compliance, focusing on immunosuppressants
MBSRQ by Brown[28]; German version by Mühlan and Schmidt[29] (additional items to evaluate potential organ fantasies [Kumnig et al, in preparation])	Questionnaire to measure body image and organ fantasies
SF-36 Health Survey by Ware et al[30]; German version by Bullinger and Kirchberger[31]	Survey to measure quality of life
TxEQ by Ziegelmann et al[32]; German version by Klaghofer et al[21,33]	Scale to measure potential posttransplant effects (eg, adherence, responsibility)

transplantation at our institute in the early stage of our program. For unilateral hand amputees, it was assumed that the remaining hand might suffice for most motoric, sensoric, and communicating functions. However, patients' functional needs and psychological impairment differ between individuals. Moreover, individual psychological distress may affect the benefit/risk ratio of the side effects caused by immunosuppression.

Therefore, the assessment of potential psychological assets and drawbacks of unilateral versus bilateral hand transplantation should include an evaluation of the patient's concept of body and self. Based on our clinical experience, the surgical restoration of a patient's damaged concept of body and self represents one of the central motivational aspects for surgery, especially in newly injured patients. In this regard, newly injured patients might be different from patients who have been living with the amputation for many years because they have learned to integrate the defect in their individual concepts of body and self and to cope with their imperfections. Some essential psychological differences between unilateral and bilateral amputees regarding motivational aspects, coping skills, compliance, concept of body and self, and quality of life should be assessed routinely by initial psychological assessment and continuous follow-up before and after hand transplantation. Particular attention should be paid to differences between candidates for unilateral and bilateral hand transplantation. Ideally, a multicenter trial investigating psychological and psychosocial aspects in candidates for unilateral and bilateral hand transplantation should be pursued to obtain information on these important aspects and to serve as the basis for development of a standardized psychological screening protocol.

SURGERY

The surgical procedures were performed by teams comprising members of the Department of Plastic Surgery and Traumatology for all transplants. As described previously for cases 1 and 2, the recipient stumps and the donor forearms were prepared simultaneously.[2,6,13] Ulnar and radial artery, 1 palmar and 2 dorsal veins, the median and ulnar nerve, and the superficial branch of the radial nerve, as well as all extensor and flexor tendons, were identified proximally and distally and marked for musculoskeletal and microsurgical vascular/neural reconstruction.

In summary, following bone fixation, arterial and venous anastomoses were performed (radial and ulnar artery and a varying number of deep and superficial veins in the individual cases).[2,6,13,37] Subsequently, all hand and finger flexor and extensor tendons were attached. The ulnar and

median nerve were coapted thereafter. Reconstruction of the radial nerve branches varied between patients. At the end of the procedure, skin flaps were approximated without tension. In patient 1, several muscles of the left forearm were insufficient or even missing, which required tendon repair en masse or by transpositioning.[2] Clinical observation and oxygen saturation monitoring confirmed patency of vessels and regular blood flow. Skin necrosis required skin grafts in all 3 bilateral hand transplant recipients. Long-term, patency of the vasculature was investigated using Doppler ultrasound.

To prevent ischemia/reperfusion injury (IRI), ischemia time was kept short in all cases. Time intervals between arteriovenous cross-clamping and reperfusion of the allograft were 150/170, 155/153, and 190/210 minutes in patients 1, 2, and 3, respectively. A short ischemia time was considered particularly important in the second case, in which a large quantity of skeletal muscle was transplanted. Allografts were flushed with cold Custodiol (HTK) or University of Wisconsin (UW) preservation solution.

Early Secondary Procedures

Split-thickness skin grafts were needed for defect coverage of the left forearm in patient 1.[2,14] Multiple arteriovenous fistulas required occlusion at 6 months after surgery. Skin grafting for wound closure was also necessary in case 2. In patient 3, 2 episodes of immediate postoperative soft tissue swelling caused by hematoma required surgical revision and defect coverage using split-thickness skin grafts at 1 week.

Late Secondary Procedures

Aesthetic scar excisions were performed in patient 2 in 2005.[14] In the third patient, surgical scar correction in the face and simultaneous scar and skin graft resection on both forearms was performed at 1 year. Two years after hand transplantation, insufficient palmar abduction and opposition of the thumb required an opponensplasty by transposing the superficial flexor tendon of the patient's ring finger.

Managing Neuromusculoskeletal Reconstruction in Forearm Transplantation

In forearm transplantation, detailed preoperative clinical, radiological, and neurologic examination is mandatory to evaluate the functional capacity of remaining neuromuscular units. Adequate length and intact innervation of the recipient's remaining musculature are critical for achieving normal functional capacity of the neuromuscular units involved. Innervated short muscular remnants may need replacement by an entire neuromuscular unit of the donor with higher vulnerability to ischemia including motor nerve coaptation. Hence a longer time frame for neuromuscular regeneration in proximal forearm transplantation has to be expected when compared with hand transplantation at the wrist level.

In patient 2, missing and insufficient muscles required replacement by neuromuscular units of the donor.[6,15] Innervated remnants of forearm muscles were left untouched for possible use of a myoelectrical prosthesis in case of graft loss (lifeboat maneuver). Flexor muscles of the donor were attached to the medial epicondyle of the humerus, ulnar extensor carpi, and extensor digitorum communis to the periosteum of the ulna. Anterior and posterior interosseus nerve, as well as the motor branches of the median nerve for pronator teres, flexor carpi radialis, flexor digitorum superficialis, and palmaris longus, were coapted. Coaptation of the ulnar nerve was performed distal to the intact motor branches of the FCU.

GRAFT MONITORING

Grafts monitoring for rejection can be performed by visual inspection. Skin biopsies were regularly taken for histopathologic and immunohistochemical investigation (protocol biopsy) or whenever skin rejection was suspected (for cause biopsies). For evaluation of bone healing, radiographs and color Doppler sonography were performed regularly during the first year after transplantation. Graft vessels, nerves, muscles, and tendons were monitored by ultrasound. In addition, angiography and computed tomography angiography with three-dimensional reconstruction of graft vessels were performed once a year for assessment of chronic vascular changes.

No complications regarding bone regeneration were reported in any patient. As reported for patient 1, bone healing after hand transplantation was not influenced or altered by immunosuppression, compared with replantation.[37,38] Vascular invasion and callus formation appeared at week 3, calcified callus was observed at 4 months after transplantation, and bone union was completed after 11 months. In patient 2, the right forearm flexors revealed signs of fibrosis and ossification, resulting in dissection of this small compartment.[6] Vascular patency of graft vessels was documented in all cases, showing stable proportions and consistent perfusion of all tissue components.[14] No radiomorphologic signs of luminal narrowing as indicators for myointimal proliferation and chronic rejection were observed. In patient

1, kinking of the ulnar and radial arteries as a result of long vessels was observed.[2] In addition, an occlusion of the right radial artery was detected at 1 year in this patient, which was found to have recanalized at 4 years after transplantation.[4]

FUNCTIONAL OUTCOME

Rehabilitation Protocol and Functional Assessment

Principles of the rehabilitation program were published previously.[2,4] In brief, the rehabilitation program was based on an early protective motion program (EPM) in combination with cognitive exercise training after Perfetti, electrostimulation, and occupational therapy and adjusted to the type of transplant (hand vs forearm), the individual patient's needs, and the level of progress. The major goal of the rehabilitation protocol was to enable independence in basic activities of daily life and hence to increase the patient's quality of life and psychological well-being. Motor function and hand sensitivity, as well as electrophysiologic studies and somatosensory evoked potentials, were studied at close intervals during the first 5 years after surgery and annually thereafter. Hand function was evaluated and documented by a variety of tests and scoring systems, as described earlier.[6]

Function

For patient 1, updates on hand function were published at 1.5, 5, and 8 years, respectively.[2,4,13,14] The progress in functional and sensory recovery was outstanding in this patient. At 4 months, intrinsic muscle activity was observed for the first time. After the first year after transplantation, the patient was able to perform activities of daily life (except buttoning a shirt[2]), and was back to work at a police station by then. At 1 year, thermal discrimination, pressure sensation, sensitivity to pain, and 2-point discrimination sensation were present in hand and fingers of the right and left allograft. Hand function and sensitivity continuously improved until year 5 after transplantation and remained stable thereafter. The patient experienced a fracture of the left radius at month 56, which resulted in a transient decrease in active range of motion at 5 years. After 5 years, total active range of motion increased and decreased for some joints, but remained stable overall.

In the forearm transplant recipient, update on functioning was given at 3, 5, and 6 years' follow-up.[6,14,15] Compared with patient 1, motor function was inferior at all time points; however, a continuous improvement in hand function was observed during the first 3 years after surgery. The patient described hand function as superior to the function he experienced with myoelectrical prostheses. Temperature discrimination was apparent for the first time at 6 months, although sensitivity overall remained poor. Dexterity was slightly inferior to that observed after hand transplantation.

In the third transplant recipient, rehabilitation was complicated by blindness. An update was provided at 2 years after transplantation.[14] At that time, the patient was still receiving intensive physiotherapy and rehabilitation. According to the Hand Transplantation Score System, functional outcome at 1 year after surgery was graded as 64 and 65.5 out of 100 for the left and the right hand, respectively.[39] Hand function improved during another year after transplantation and signs of intrinsic muscle recovery were detected by then.

Nerve conduction studies revealed that motor and also sensory action potentials not only increased by an early time point after transplantation but also after 4–5 years after transplantation.[14] These findings show that nerve regeneration can also be expected at later periods after hand transplantation.

IMMUNOSUPPRESSION AND IMMUNOLOGIC COMPLICATIONS

Immunosuppression

Induction therapy with antithymocyte globulin (ATG) was used in the first 2 patients and alemtuzumab (Campath-1H) in the third patient. Tacrolimus, prednisone, and mycophenolate mofetil (MMF) were used for maintenance. Tacrolimus trough levels of 15 ng/mL were targeted during the first month and reduced thereafter. Steroids were tapered in a stepwise fashion and withdrawn in patients 1 and 2 between year 3 and 5. In patient 1, sirolimus was started at 2 years and tacrolimus was eventually withdrawn at 5 years. In patients 2 and 3, everolimus was added to the maintenance IS and tacrolimus is currently being weaned.[4,6,14]

Rejection Episodes, Treatment and Current Immunosuppression

All patients experienced at least 1 acute rejection episode within the first year after transplantation. The onset of the first rejection episode was at postoperative day 55, 9, and 51 in patients 1, 2, and 3 respectively.[14] A total of 3, 6, and 4 rejection episodes were observed. The appearance of the skin lesions was mostly scattered, nonconfluent, and restricted to a defined region either on the forearm of dorsum of the hand. However, a characteristic pattern of rejection was observed for each patient.

Patient 1 experienced only 2 mild rejections[2,4] (grade 1–2). Treatment with topical tacrolimus and steroid ointments, intravenous (IV) steroids, and restart of tacrolimus treatment for 8 months (after tacrolimus had been withdrawn) were effective. The postoperative course of the forearm transplant recipient (patient 2) was challenged by increasingly severe rejections compared with patient 1. A comprehensive report on this topic is given elsewhere.[6,14,40] In brief, 2 mild rejection episodes occurred on days 9 and 46 followed by severe (grade IV and III) rejections on days 95 and 345 and 2 more mild (grade I) rejections on days 473 and 972. Therapy included IV steroids, topical steroids, basiliximab, ATG, and alemtuzumab. In patient 3, a first rejection was observed on day 51 (grade 2) followed by a rejection grade 3 that was restricted to the palm on day 60 and a rejection grade 2 on day 601.[14] Although the first rejection responded promptly to IV steroids, the second episode required administration of alemtuzumab. A detailed report of the second, atypical rejection episode was published earlier.[39] No donor cells were found in the blood of any recipient during the follow-up period, indicating that no chimerism is induced with hand or forearm transplantation and conventional immunosuppressive therapy.[14]

COMPLICATIONS AND SIDE EFFECTS

Aggressive immunosuppressive regimens have been used in hand transplantation and an intensified treatment is necessary on rejection. Infectious prophylaxis consisted of piperacillin/tazobactam (patient 1, 2) or amoxicillin/clavulanic acid (patient 3), fluconazole (patient 2), ganciclovir (patient 1) or ganciclovir/valganciclovir (patients 2 and 3) and trimetoprim/sulfametoxazole (given during the first year in all patients).

As published earlier,[41,42] cytomegalovirus (CMV)-associated disease was detected in all 3 double hand allograft recipients. The donor/recipient CMV combination was d+/r−, d+/r+, and d+/r+ for patients 1, 2, and 3 respectively. In the first 2 patients, CMV infection was resistant to valgancyclovir but controlled with anti-CMV hyperimmunoglobulin, foscarnet, and cidofovir. Because of foscarnet treatment, patient 1 experienced nausea and diarrhea, and patient 2 developed severe neutropenia triggered by valgancylovir around day 150. Cidofovir and anti-CMV hyperimmunoglobulin treatment resulted in edema of both transplanted hands in the second case. The third patient experienced repetitive, but mild, CMV infections, which were successfully treated with valgancyclovir. In the forearm recipient, an invasive fungal infection and human papilloma virus (HPV)–associated skin warts scattered over the thumbs of the allografts required treatment. Noninfectious side effects included hypertension (patient 2, 3) resulting in severe headaches in patient 2, a transient increase of creatinine levels (patient 1, 2, 3), non–insulin-dependent diabetes mellitus (patient 1), and hyperlipidemia (patient 2, 3). After repeated administration of alemtuzumab because of severe rejection episodes, patient 3 developed nausea, fever, headache, and edema requiring hospitalization and monitoring of hemodynamic parameters.

DISCUSSION

In summary, good functional results and a high degree of patient satisfaction have been achieved with bilateral hand transplantation in Innsbruck. Acute rejection episodes, especially during an early period, are common complications; this was also recorded in the latest update of The International Registry of Hand and Composite Tissue Transplantation.[43] The follow-up of approximately 80% of recipients was challenged by an acute rejection episode before year 1 after transplantation. Although immunosuppressive regimens were more aggressive during the early period, moderate-dose to low-dose IS protocols were successful in preventing additional rejections and graft loss in all 3 cases. Weaning from steroids, tapering IS trough levels, and conversion from calcineurin inhibitors to mammalian target of rapamycin (mTOR) inhibitors seems possible in all patients.

No radiomorphologic changes in graft bone, muscular texture, and nerve anastomoses were detected in any patient. Vascular changes were observed rarely and only 1 minor complication required further intervention. Monitoring for chronic vascular changes is of utmost importance. So far, no evidence of chronic vascular changes have been observed in any patient transplanted in Innsbruck.

Infections are common complications observed after reconstructive transplantation, especially on intensified IS. Early and accurate diagnosis, as well as specific treatment, is required in these cases. IS-sparing protocols might help to reduce complications and side effects.

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