Upper extremity transplantation: current concepts and challenges in an emerging field

River M. Elliott · Scott M. Tintle · L. Scott Levin

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Abstract Loss of an isolated upper limb is an emotionally and physically devastating event that results in significant impairment. Patients who lose both upper extremities experience profound disability that affects nearly every aspect of their lives. While prosthetics and surgery can eventually provide the single limb amputee with a suitable assisting hand, limited utility, minimal haptic feedback, weight, and discomfort are persistent problems with these techniques that contribute to high rates of prosthetic rejection. Moreover, despite ongoing advances in prosthetic technology, bilateral amputees continue to experience high levels of dependency, disability, and distress. Hand and upper extremity transplantation holds several advantages over prosthetic rehabilitation. The missing limb is replaced with one of similar skin color and size. Sensibility, voluntary motor control, and proprioception are restored to a greater degree, and afford better dexterity and function than prosthetics. The main shortcomings of transplantation include the hazards of immunosuppression, the complications of rejection and its treatment, and high cost. Hand and upper limb transplantation represents the most commonly performed surgery in the growing field of Vascularized Composite Allotransplantation (VCA). As upper limb transplantation and VCA have become more widespread,

several important challenges and controversies have emerged. These include: refining indications for transplantation, optimizing immunosuppression, establishing reliable criteria for monitoring, diagnosing, and treating rejection, and standardizing outcome measures. This article will summarize the historical background of hand transplantation and review the current literature and concepts surrounding it.

Keywords Hand transplantation · Vascularized composite allotransplantation · Hand reconstruction

Introduction

Hands are the fundamental instruments through which humans shape their environment. Loss of 1 hand is, therefore, catastrophic. Loss of both hands results in severe disability that frequently requires a caregiver to assist in basic grooming, self-care, and other activities of daily living [1]. For adults accustomed to independence and work, the effect of these injuries can be both psychologically and physically debilitating [2].

Traditionally, prosthetics have formed the mainstay of treatment for upper extremity amputees. Simple body-powered prosthetics are cost effective, but patients often reject them because of discomfort, weight, or limited usefulness [3]. The newer generation of myoelectric prostheses feature improved voluntary control and are capable of more complex and forceful motion, but are exceedingly more expensive, less durable, and noticeably heavier than a body-powered prosthesis.

As part of the rapidly developing field of VCA, hand and upper extremity transplantation has the potential to replace the missing hand or arm with a nearly identical sensate limb capable of complex manipulation. Theoretically, by transplanting the entire part along with its nerves, blood

R. M. Elliott
The Curtis National Hand Center, 3333 North Calvert Street,
Baltimore, MD 21209, USA

S. M. Tintle
Department of Orthopaedic Surgery, Walter Reed National Military
Medical Center, America Building, 19 2nd Floor, Bethesda,
MD 20889-5600, USA

L. S. Levin (✉)
Department of Orthopaedic Surgery, Hospital of the University of
Pennsylvania, 2 Silverstein, 3400 Spruce Street, Philadelphia,
PA 19104, USA
e-mail: scott.levin@uphs.upenn.edu

vessels, muscle and tendon units, and bone, VCA can accomplish reconstructive results far superior to those of the most advanced surgical techniques or prosthetic technologies. The ultimate goal is replacement of the missing limb with one that is nearly identical in both function and appearance. The potential advantages over conventional reconstruction and prosthetics are obvious, but given the risks of lifelong immunosuppression, the high monetary cost, and other important factors, these operations are reserved for cases characterized by severe psychological and physical disability.

As upper extremity transplantation has become more commonplace, several important problems have emerged. These include optimization of the immunosuppressive regimen, establishing outcomes measures that are applicable to these operations, refining criteria for patient selection, minimizing costs, improving operative efficiency, and enhancing reinnervation of the graft, to name but a few. This article will review the history of hand and upper extremity transplantation and will discuss the new challenges and current practice pertaining to this promising field.

History

Hand transplantation developed from the convergence of 2 seemingly disparate fields: hand surgery and solid organ transplantation. The essential surgical techniques necessary to perform a successful transplantation—namely osteosynthesis, tendon repair, nerve coaptation, and microvascular surgery—all originated from hand surgeons' experience in replantation and treatment of mutilating hand injuries. From solid organ transplantation came the discovery and clinical application of immunosuppressive therapies, as well as the creation of multidisciplinary treatment teams critical to the preoperative assessment and postoperative care of the patient.

VCA's origins are deeply rooted in upper extremity surgery. In fact, Dr. Earl E. Peacock Jr. coined the phrase "composite tissue allograft" in 1957 when describing his technique of using cadaveric flexor tendons and sheaths to reconstruct end-stage tendon incarcerations [4–7]. The introduction of first generation immunosuppressive drugs and the success of renal allotransplantation in the early 1960s seemed to establish the groundwork for upper extremity allografts. In 1964, the world's first hand transplant was performed in Ecuador, when Dr. Robert Gilbert transplanted a single hand onto a bilateral amputee. The postoperative use of prednisone and azathioprine, therapies that had made renal allografts feasible, failed to prevent acute rejection in this patient, and the graft was amputated 3 weeks after surgery [8]. This failure, as well as similar outcomes in small animal models, tempered any initial enthusiasm for VCA. While solid organ transplantation flourished, another attempt at hand transplantation would not take place for another 3 decades.

These early failures lead to a consensus view that limb and other composite allografts were too immunogenic to safely transplant, owing to the large amount of skin and lymphatic tissue that they contain. More effective immunosuppressive therapy was needed to prevent acute rejection. In the 1980s and 1990s, the discovery of calcineurin inhibitors, cyclosporine, mycophenolate mofetil (MMF), and the use of induction therapy, transformed the field of solid organ transplantation. Meanwhile, use of these agents in small animal VCA models demonstrated that composite allografts might be feasible in humans [9–11].

In Lyon, France, a group of surgeons lead by Jean-Michel Dubernard performed the first transplant of the modern era in 1998. Although the procedure was successful in a technical sense, the patient was unable to psychologically adjust to the new limb and stopped taking his immunosuppressive medications and ceased participating in physical therapy. His transplanted limb was eventually amputated [12, 13]. This unfortunate result demonstrated how psychiatric evaluation, patient selection, and compliance with postoperative medication and physical therapy ultimately have as much to do with the survival of the allograft as surgical technique. In 1999, Warren Breidenbach led a team of surgeons in a fourteen and a half-hour surgery at the University of Louisville in what would ultimately be the first American upper extremity transplant [14]. This patient is currently the longest surviving hand transplant recipient in the world [15].

Shortly thereafter, the Lyon group established another milestone, performing the world's first bilateral hand transplant in early 2000 [16]. In the ensuing years, hand transplantation, while still rare, has become increasingly common. Worldwide, more than 70 transplants have been performed. In the United States alone, transplants have been performed at the University of Louisville, the University of Pittsburgh, the University of California, Los Angeles, Harvard University, The University of Pennsylvania, Emory University, Johns Hopkins University, and Lackland Air Force Base.

Current practice and emerging challenges

Indications and patient selection

Solid organ transplantation is truly a life-saving procedure, and therefore is not subject to the same ethical considerations that surround VCA. In other words, a patient receiving an organ transplant will perish without it, and this fact alone justifies the inherent risks of the surgery as well as the dangers of lifelong immunosuppression. Hand transplantation, however, does not prolong life but merely improves it. The patient receiving a hand transplant will also be exposed to the risks of immunosuppression, and because of this may very well live a shorter life than he or she would otherwise. Given the current

state of drug therapy, the ethical calculus of performing an upper extremity transplant involves weighing the benefit of improved quality of life against the cost of lifelong immunosuppression and the risks of surgery. These are difficult decisions to make, and can vary greatly depending on the extent of disability and the functional demands of the potential recipient. In addition, lack of a formalized system of outcome measures and long-term results in a large number of patients makes an estimation of the benefits of these surgeries difficult.

For these reasons, indications for hand transplantation have remained highly individualized to both the recipient and the performing institution. Autonomy, both on the institutional and patient level, remains a priority. To date there has been no established consensus on specific indications for upper extremity transplantation, but as the field continues to grow, so too does the need for an established set of clinical criteria [17].

In 2008 the American Society for Reconstructive Transplantation (ASRT) was founded for the purpose of advancing the science and clinical practice of VCA. The ASRT recently developed a series of clinical criteria and contraindications pertaining to upper extremity transplantation that provide a useful foundation for the eventual creation of more specific indications. The basic clinical criteria for hand transplantation established by the ASRT include amputation or irreversible functional loss and:

- A comprehensive medical history and physical exam conducted by a hand surgeon to evaluate the need for transplantation.
- A surgical treatment plan that outlines the surgical approach and the prognosis for improvement of clinical signs/symptoms pertinent to the diagnosis has been developed.
- A comprehensive medical history and physical exam conducted by a transplant physician or surgeon to evaluate the medical ability of the patient to undergo transplantation.
- A comprehensive social and psychological exam has been performed to evaluate the motivation and ability of the patient to successfully manage a VCA allograft.
- The patient is generally over 18 years of age and has had inadequate functional recovery with conventional reconstructive surgical treatment and/or non-surgical rehabilitation.
- The amputation or loss of function is accompanied by medical or functional complications, demonstrable loss of quality of life as determined by psychological evaluation, and may or may not include tissue necrosis or ulcerations of the extremity unresponsive to nonsurgical treatments.
- Comorbid etiologies of the symptoms have been considered and ruled out.

In addition the ASRT also included a set of contraindications to transplant. These include:

- Unilateral amputees with no evidence of significant functional, social, or financial impairment as a result of their amputation.
- Congenital amputees.
- Pediatric traumatic amputees.

In order to fully understand the risks of the procedure, as well as the potential improvement in quality of life, better outcome studies and measures are needed. Delineating an objective set of successful postoperative functional criteria, cataloguing risk, and identifying patient related factors that contribute to the ultimate success or failure of a transplant will help refine the indications for these procedures. The following section will discuss this in more detail.

Outcomes

Hand transplantation remains an uncommon procedure, and has been performed at many different institutions throughout the world. Surgical protocols, recipient medical comorbidities, level of amputation, immunosuppressive regimens, and other important factors vary widely. Because this group of patients is so heterogeneous, drawing a meaningful conclusion about expected outcomes and standardizing treatment protocols is difficult.

In May 2002 the International Registry on Hand and Composite Tissue Transplantation (IRHCTT) was established to compile clinical information and track outcomes through a centralized and transparent database [18]. The most recent comprehensive data from the IRHCTT was published in 2010, with an additional partial update in 2011 that reported on 57 transplants in 39 patients (18 transplants were bilateral, while 21 were unilateral) [19•]. According to this report, follow-up time ranged from 6 months to 13 years. Of the 39 patients receiving transplants, 32 were male and 7 were female. The majority (57.9 %) of transplants were performed at the wrist level, and all patients received postoperative immunosuppressive therapy consisting of tacrolimus, mycophenolate mofetil, and a steroid. Induction was performed with mono- or polyclonal antithymocyte antibodies in all cases [19•].

The IRHCTT also found that 85 % of VCA recipients (including face transplants) experienced an episode of acute rejection within 1 year of transplant. In some cases, rejection was associated with periods of non-compliance with medication or a planned decrease in immunosuppressive treatment [18]. Some patients experienced more than 1 episode of rejection, however, all cases of rejection resolved with treatment. Treatment of rejection usually involved increasing the doses of the patient's immunosuppressive drugs and/or using intravenous steroids. The 2011 IRHCTT report also found that metabolic complications occurred in 90 % (35 of 39) of

patients receiving a hand transplant, while opportunistic infections occurred in 77 % (30 of 39 patients) [19•].

As of 2011, there have been 5 graft losses in 57 transplants. Two grafts were lost on postoperative day 5 in a bilateral hand and face recipient who subsequently expired on postoperative day 65 from cerebral anoxia. This also accounts for the single death in the series. Other patients lost grafts on day 45 (infection), day 275 (intimal hyperplasia possibly due to chronic rejection), and at 29 months (non-compliance with medications and poor function).

Functional outcomes have been encouraging. All patients with surviving allografts developed protective sensation. Of these patients, 90 % developed tactile sensibility and 82 % developed discriminative sensibility [19•]. Because sensibility may continue to recover over several years, these numbers may improve as follow-up time increases. Motor recovery, as expected, proceeds in a proximal to distal direction, with extrinsic recovery occurring first. This allows the patient to begin pinch and grip activities soon after surgery in cases where distal transplants are performed. Intrinsic recovery occurs between 9–15 months, depending on the level of transplant, and has been confirmed by EMG (electromyogram). Isolated reports have documented ongoing motor and sensory recovery in hand transplant patients as late as 5 years after surgery [20]. In the 2011 update from the IRHCTT, patients recovered sufficient motor function to allow them to perform most activities of daily living, including eating, driving, grooming, and writing. In long-term follow-up of 8 and 6 years, 2 patients from the Louisville program were both able to return to work, and both reported higher functional scores than would be expected with prostheses [15]. To a degree, the level of transplant may determine how much motor and sensory function recovers after surgery, with better outcomes expected in more distal transplants. However, a limited number of above-elbow transplantations have been performed, with reasonable results [21, 22].

In order to justify the risks of immunosuppression and surgery, patients receiving hand transplants must demonstrate improved quality of life as well as improved function. To date, this critically important area remains underreported in the hand transplant literature. Jensen and colleagues reviewed 27 articles that described quality of life measures in hand transplant recipients. Outcomes were assessed using either the Disabilities of the Arm, Shoulder, and Hand (DASH) score, the Hand Transplant Score System (HTSS), or the Medical Outcomes Study Short Form-36. Most patients reported an improvement in quality of life as measured by these validated instruments, while other studies reported a qualitative improvement in quality of life, social acceptance, and appearance [23]. The IRHCTT currently uses the DASH and HTSS scores to report quality of life outcomes. Based on data from the 2010 report, quality of life improved in 75 % of

patients, and most were able to return to work. HTSS scores averaged 52 at 1 year and 88 at 10 years following transplant (in the HTSS score, 100 is the highest possible score). DASH scores averaged 38 at 1 year and 16 at 10 years post-transplant (in the DASH score, 0 is the best possible score) [18]. Currently, the true benefits and psychological repercussions of hand transplantation are poorly understood. Future studies should develop validated instruments that more accurately assess the change in quality of life that these patients experience.

Basic science

Immunosuppression

Hand transplants are made of up composite tissue, including skin, muscle, nerve, tendon, and bone. This makes their immunologic profile strikingly different from solid organ transplants. Skin, in particular, is known to be highly antigenic [24]. Preventing the recipient from rejecting the cutaneous portion of the composite allograft has historically required high doses of multidrug immunosuppressive therapy, and concern over the long-term effects of such therapy has been a major impediment to the growth of hand transplantation [25]. The known risks of chronic immunosuppression include opportunistic infection, malignancy (skin neoplasms in particular), metabolic derangements including diabetes and hyperlipidemia, nephrotoxicity, neurotoxicity, wound healing problems, and others. These drugs are also expensive, which is a major factor in patient non-compliance and an important consideration in the current political climate of medical cost containment.

As mentioned previously, current immunosuppressive therapy usually consists of a multidrug regimen of tacrolimus, mycophenolate mofetil, and a steroid. Induction therapy, aimed at depleting the recipient's immune response and preventing acute rejection, is usually given in several doses, and typically is either a polyclonal or monoclonal antibody directed against thymocytes. These therapies have been derived from protocols that are well established within solid organ transplantation, and most centers have reported using dosages and serum levels of immunosuppressive medications at levels similar to or slightly higher than a renal transplant [26]. Compiled data from the IRHCTT indicate that the majority (85 %) of hand transplant recipients experience at least 1 episode of acute rejection following transplant. Clinically, acute rejection is typically seen as an erythematous maculopapular rash, although subtle findings such as hair loss or desquamation at the fingers may be indicators a more chronic or insidious process. Monitoring therefore, is a

relatively straightforward process of observing the patient's skin. Biopsy findings of acute rejection include lymphocytic infiltrates typically seen in solid organ transplants [27]. Histologic evidence of chronic rejection has not been identified, but is thought to involve intimal hyperplasia [18].

Because the risks of lifelong immunosuppression restrain the growth of VCA, novel strategies directed toward reduction of immunosuppression or modulation of the recipient's immune system are now areas of intense scientific interest. Steroid sparing protocols, common in solid organ transplantation, have been attempted in hand transplantation, as have protocols using sirolimus in lieu of tacrolimus [26]. Investigators have also attempted to use topical steroids or tacrolimus in an effort to either treat acute rejection or reduce the overall amount of systemic immunosuppression [18, 28, 29]. This therapy is based on the still controversial assumption that the skin drives the antigenic response from the host, and that muscle, tendon, and nerve are relatively spared during episodes of rejection.

Altering the recipient's immune system, or immunomodulation, is another promising means of reducing or outright eliminating the need for multidrug therapy. Prior work in solid organ transplants, wherein donor bone marrow cells are infused as part of induction therapy, has been directed towards creating a state of immunologic chimerism in the recipient [30•, 31–34]. Chimerism represents a critical step in including tolerance of donor antigens in the recipient. Prior studies have demonstrated that small amounts of circulating donor lymphocytes, representing microchimerism, are sufficient to induce tolerance in the host [35, 36]. Since upper extremity transplants often involve transplantation of vascularized bone marrow as well, the potential to induce chimerism in these patients is greater than in solid organs.

Human trials in cell-based therapy have been performed at the University of Pittsburgh under the direction of Dr. Andrew Lee (now at Johns Hopkins). In a total of 5 patients, bone marrow was infused as part of an overall strategy to induce tolerance through chimerism. Alemtuzumab and prednisone were used for induction therapy, and tacrolimus alone for monotherapy. Donor bone marrow cells were infused on day 14 [30•]. Although all patients experienced acute rejection, these episodes were successfully treated with intravenous steroids or topical tacrolimus and steroids. This limited trial demonstrated that, following donor bone marrow infusion, human composite allografts could be maintained using tacrolimus monotherapy alone [30•]. While further trials in larger numbers of patients are needed, the early results for cell-based immunomodulation appear promising.

Nerve regeneration

Unlike solid organ transplants, a composite allograft must not only survive, but also it must function well to be considered

successful. In the upper extremity, nerve regeneration progresses at roughly 1 mm per day [37]. For proximal transplants, this slow rate of growth means that distal muscles may become fibrotic and useless well before they can be re-innervated. This may compromise the overall functional outcome of an otherwise successful transplant, and is a major reason why proximal forearm and above-elbow transplants remain controversial. For these reasons, augmenting nerve regeneration, whether through cell-based or pharmacologic mechanisms, has become another important area of inquiry.

Fortunately, tacrolimus has been shown to enhance nerve regeneration through signaling pathways independent from calcineurin inhibition [38]. In other words, the drugs that transplant surgeons rely on to stave off rejection also have the beneficial property of stimulating nerve regrowth. In animal models, tacrolimus has been shown to enhance nerve recovery in direct nerve transection as well as nerve reconstruction with grafts [39, 40]. In humans, limited clinical studies in human nerve allografts have demonstrated enhanced recovery as well [41]. There is also a growing body of evidence that cell-based therapies utilizing bone marrow derived mesenchymal stem cells may also play a significant role in inducing tolerance as well as enhancing nerve recovery [26].

Conclusions

Hand transplantation has become an increasingly common means of delivering life-restoring treatment to patients afflicted with devastating and disabling injuries. High rates of initial success, coupled with growing global interest in VCA, have led to increasing numbers of transplants worldwide. In order for hand transplantation to become accepted in the same way that solid organ transplants have, several important challenges must be addressed. Clinically, better outcome studies and accepted standards of clinical success must be developed. At the same time, clearer indications for these surgeries are needed. At present, the lifelong requirement for high dose immunosuppression and its attendant risks present a major barrier to growth.

Compliance with Ethics Guidelines

Conflict of Interest River M. Elliott declares that he has no conflict of interest. Scott M. Tintle declares that he has no conflict of interest. L. Scott Levin declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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