IFSSH Scientific Committee on Hand Transplantation

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Hand Transplantation

Introduction

Over the past decade, hand transplantation has become an established means of limb reconstruction for patients with severe injuries to the hand and forearm. Hand transplantation, like face transplantation, is a form of vascularized composite allotransplantation (VCA). Similar to solid organ transplantation, VCA consists of the transfer of living tissue from a donor to the recipient. The patient requires standard immunosuppression to prevent rejection. Unlike solid organ transplantation, nerve regeneration into the transplanted tissue is required for sensation within the skin and re-animation of muscles within the transplanted tissue. Since 1998 over 60 hand transplants have been performed successfully around the world. This manuscript will provide a brief overview of the current state of hand transplantation.

Background

The first attempt at hand transplantation occurred in Ecuador in 1964 by Gilbert but failed due to problems with inadequate immunosuppression.[5, 6] Over the past 2 decades immunosuppressive medications have substantially improved with the development of calcineurin inhibitors, FK-506 (Tacrolimus) and mycophenolate mofetil (MMF). These medications have allowed for improvement in solid organ transplantation and for longterm survival of limb transplant models in animal models.[7-9] Since 1998 a worldwide registry was created to track patient progress following VCA and report outcomes.[12].

International Registry of Hand and Composite Tissue Transplantation (IRHTCC)

The most extensive and comprehensive outcome data regarding hand transplantation was published by the International Registry of Hand and Composite Tissue Transplantation (IRHTCC) in 2010. At that time, followup was available on 33 patients who had undergone 49 hand transplants (17 unilateral and 16 bilateral transplants) and 2 digits. Patients who have elected to undergo hand transplant have tended to be younger individuals, with an average age of 32 years (range 19–54yrs). Follow-up within the IRHTCC report extended from 1 months to 11 years.[13, 14] The majority of patients were male. Time from original injury to transplant varied from 2 months to 34 years[13]. The cause of the majority of amputations has been trauma.

Within the IRHTCC study, graft survival was 100% at 1 and 2 years following transplantation[12]. Within the European and American experience, current long-term

graft survival is better than 94%. Immunitymediated rejection has been the primary cause of graft loss. [12, 14]. The first case of graft loss occurred with the first unilateral hand transplant patient in 1998; pathologic specimens of the rejected hand showed evidence of lichenoid like lesions, which can also be seen in cases of graft versus host disease[12, 13]. The rejection occurred after the patient stopped taking his immunosuppression medications despite a well-functioning hand. The second case of graft loss occurred in an American patient transplanted in Louisville as a result of chronic rejection. The cause of the American patient's rejection is thought to be related to fibro-intimal hyperplasia, a mechanism of rejection which can be seen in cases of heart transplant rejection [15].

The choice of immunosuppression has been an issue of some debate but the majority of hand transplant procedures have involved an induction process consisting of antithymocyte globin (ATG), tacrolimus, MMF and steroids. Maintenance therapy for the majority of patients has been continuation of MMF, tacrolimus and steroids; this triple drug combination is similar to what is currently used as standard treatment in solid organ transplantation[12, 16, 17]. Modifications of this triple therapy have been reported, and in the IRHTCC study, 21.7% of recipients received only steroids and tacrolimus for maintenance therapy, whereas 8.7% of recipients were switched to sirolimus; 8.7% of recipients received steroids, low dose tacrolimus, and everolimus, 4.3% received sirolimus and MMF. 13% of patients underwent withdrawal of steroids at some point during the follow-up period[12, 13]. Substitutions for tacrolimus (to sirolimus or everlimus) are usually related to the patient's tolerance to the medication.

The desire for minimizing steroid dosing in these patients is related to the unwanted side effects of the medications. Cushing syndrome, weight gain, dermatitis and mood swings have also been observed and have been attributed to the use of steroids. Metabolic complications have been seen in up to 50% of patients and have included hyperglycemia and increase in creatinine values. Most of these adverse effects have been transient and reversible. One patient has required bilateral hip joint replacements; however, at the time of the IRHTCC study all patients' serum creatinine levels were inferior or equal to 1.4mg/dL (eight recipients inferior or equal to 1 mg/dL). At this time point no malignancies or life-threatening conditions have been reported[12, 13].

The majority of patients (87%) have developed opportunistic infections which have includes CMV, Clostridium, and herpetic infections. The incidence of metabolic complications and opportunistic infections appears to be similar to that of solid organ transplantation. Newer protocols of steroid tapering or steroid sparing therapies have been tried in addition to new antilymphocytic agents, but it is still too early to assess any benefit of these protocols over "standard immunosuppression."[12, 18].

Despite immunosuppression, acute rejection episodes occurred in 85% of the patients within the first year; however all episodes of acute rejection were controlled with modifications of immunosuppressive medications. Acute rejection, in cases of hand transplantation, is evaluated with the use of skin biopsies. Rejection episodes are usually heralded by the development of a rash or dermatitis, alerting the patient to seek medical attention. Skin biopsies show evidence of lymphocytic infiltration in cases of acute rejection. Rejection episodes and their management are similar to those of solid organs and appear to have better survival rates than solid organs when immunosuppressive protocols are followed properly[18, 19]. The majority of acute rejection episodes may be managed with the use of topical or systemic steroid and topical tacrolimus[12]. Deterioration in hand function has not been noted following rejection episodes. [12, 17] Functional outcomes have been very encouraging with all patients recovering protective sensibility, 90% recovering tactile sensibility, and 82.3% recovering discriminative sensibility [14]. Muscle recovery begins with the extrinsic flexor and extensor groups, allowing some patients to perform grasp and pinch activities shortly after transplantation. Recovery of intrinsic muscles can take up to 9 and 15 months post transplantation. Recovery of intrinsic muscle function has been confirmed by electromyographic studies in several hands [16, 19]. Extrinsic and intrinsic muscle function has allowed patients to perform most daily activities, including eating, driving, grasping objects, riding a bicycle or motorbike, shaving, using the telephone and writing. Patient quality of life scores improved significantly in more than 75% of the recipients. Bilateral hand transplanted recipients were only slightly more satisfied than unilateral hand transplant patients. Returning to work has been a consistent feature for the majority of the patients [13, 17].[14] Functional MRI has demonstrated that after transplantation, hand representation is regained within the sensory and motor cortex within the brain [20, 21].

Brandacher and colleagues reported that the most significant clinical improvements occur during the first three years following transplant, with minor improvements occurring after that. Discriminative sensation has been identified in all forearm transplantations and gives great hope to patient with very high disabling injuries[17]. Nerve recovery in traumatic injuries is thought to recover at a rate of 1mm a day from the point of injury. Thus the more proximal the transplantation the longer the time required to recover sensation within the hand. Interestingly, it has been noted that tacrolimus, one of the immunosuppressive medications commonly used in hand transplantation, has been able to accelerate nerve recovery, potentially shortening the period of time necessary for sensory return within the hand [22].

In summary, the IRHTCC report shows that after 9 years of clinical follow-up hand transplantation is technically feasible and that results are encouraging. Major adverse effects because of immunosuppressive medications did not occur. Immunosuppressive protocols currently used in solid organ transplantation turned out to be sufficient to prevent rejection after hand transplantation. From a functional point of view, a

remarkably good recovery of sensibility has been documented in all transplanted hands. In particular, protective sensation was achieved in all patients within 6 to 12 months and, as time progressed, 90% showed tactile and 72% of the discriminative sensibility, thus providing a true benefit over prosthetic wear [12, 13].

References

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