REVIEW PAPER

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Hand Transplantation: Current concepts and management algorithm

Trasplante de mano: conceptos actuales y algoritmo de manejo

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| Abstract |

Introduction: Hand transplantation was first reported in 1964, and is currently one of the challenges that the 21st century poses to Medicine. Several related studies and advances have been achieved, thus allowing to explore new alternatives for patient management. Many reference centers have performed their own analyzes based on their experience, which has led to increase the viability of this type of transplant.

Objective: This review seeks to provide an overview of hand transplantation and to propose a management algorithm.

Materials and methods: Several criteria must be met to select candidates, including clinical, paraclinical and psychosocial assessment performed by a multidisciplinary team. Immunosuppression seeks to avoid rejection, while immunosuppressants must have appropriate serum levels to reduce adverse effects. Classical and atypical acute rejection cases have been reported, where the skin is the main target tissue. Chronic rejection cases are related to the blood vessels that become affected. Monitoring is performed using several tests, considering skin biopsy as the gold standard.

Results: Drug therapy complications derive from drug toxicity, which are manifested as metabolic disorders, development of opportunistic infections and neoplasms. Rehabilitation and social aspects, such as patient satisfaction, should be evaluated during recovery to ensure adherence to immunosuppressive therapy. In 2011, the international registry of hand and composite tissue transplantation reported 39 cases of upper limb transplantation with multiple results. All this proves that to achieve optimal and viable results, a multidisciplinary team must conduct proper follow-up, and that the patient should have a support and motivation network, and comply with pharmacological management.

Conclusion: Further research is expected to create strategies to develop tolerance and, thus, reduce management by immunosuppression.

Keywords: Hand Transplantation; Immunosuppression; Composite Tissue Allografts; Graft Rejection; Infection.

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| Resumen |

Introducción. El trasplante de mano ha sido uno de los retos del siglo XXI, cuyo primer caso reportado ocurrió en 1964. En este campo se han hecho estudios y avances que permitieron explorar nuevas alternativas para el manejo del paciente con trasplante de mano, por lo que diversos centros de referencia han realizado análisis basados en sus experiencias, las cuales permitieron lograr la viabilidad de este tipo de trasplante.

Objetivo. Esta revisión busca dar una visión general sobre el trasplante de mano y proponer un algoritmo de manejo.

Materiales y métodos. La selección de candidatos requiere una serie de criterios, tales como evaluación clínica, paraclínica y psicosocial, desarrollados por un equipo multidisciplinario. La inmunosupresión busca evitar el rechazo y los inmunosupresores deben tener los niveles séricos apropiados para reducir sus efectos adversos. Se han reportado casos de rechazo agudo clásico y atípico, donde la piel es el principal tejido blanco, y rechazo crónico, en el cual se afectan los vasos sanguíneos. El seguimiento se realiza con varias pruebas, de modo que la de oro es la biopsia de piel.

Resultados. Las complicaciones del tratamiento farmacológico derivan de la toxicidad de los medicamentos y se manifiestan como alteraciones metabólicas, infecciones oportunistas y neoplasias. La rehabilitación y los aspectos sociales, como el grado de satisfacción del paciente, deben ser evaluados durante la recuperación para asegurar adherencia al tratamiento. En 2011 el registro internacional de alotransplante compuesto de mano reportó 39 casos de trasplante de extremidades superiores con resultados variables; todo esto evidencia que para lograr un resultado óptimo y viable del trasplante debe realizarse seguimiento por un equipo multidisciplinario, red de apoyo del paciente y motivación del mismo, junto con el cumplimiento del manejo farmacológico.

Conclusión. Se espera que nuevas investigaciones puedan crear estrategias para desarrollar tolerancia y, de esta forma, reducir el manejo mediante inmunosupresión.

Palabras clave: Trasplante de mano; Inmunosupresión; Alotrasplante compuesto vascularizado; Rechazo de injerto; Infección (DeCS).

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Introduction

Hand transplantation is categorized as vascularized composite allotransplantation (VCA) (1), and is different from solid organ transplantation (SOT), whose histological composition homogeneity is greater, and functionality occurs since the moment the transplantation takes place. In the case of VCA, transplantation consists of tissues such as skin, bone, muscle, tendons, nerves and blood vessels (2) that generate greater antigenic heterogeneity.

Although the survival of the recipient does not depend on VCA, as in most SOT cases, both improve the quality of life of patients (3). Despite these differences, VCA was equated to SOT in France as per Act 800 of August 6, 2004 (4). Furthermore, the U.S. Department of Health and Human Services published its decision to recognize VCA as organs (5). This decision was based on the following criteria: a) vca is vascularized and requires surgical anastomosis after transplantation; b) it is composed of multiple tissues; c) it must be recovered from a donor as an anatomical unit; d) it is transplanted into a recipient as an anatomical unit; e) it requires minimal manipulation; f) its use is homologous; g) it is not combined with devices or other elements; h) it is susceptible to ischemia, and i) it is susceptible to rejection (5). Additionally, the changes proposed to the National Organ Transplant Act in the United States would facilitate the hand donation and transplantation process (6).

Several reports on limb and face transplantation showed that VAC is more akin to SOT than to tissue transplantation (7-9). By the same token, the organ and tissue transplantation line of Universidad Nacional de Colombia considers that VAC should be treated as a solid organ. This procedure requires health personnel trained in transplantation to standardize management, and to open new scenarios for the application of organ transplantation (10).

History of hand transplantation

In 1964, Gilbert (11), ten years after the first successful kidney transplantation (12), performed the first hand transplantation in Ecuador. The procedure consisted of a unilateral graft transplant, and immunosuppressive management with azathioprine and prednisone to achieve graft survival for three weeks only (13). Due to these unsuccessful results, research on this field was halted for about three decades. Then, in 1998, a second attempt was made in Lyon (14); this time, the graft was removed 29 months after transplantation due to rejection caused by lack of adherence to treatment. In any case, these results allowed a new period for hand transplantation in the 21st century.

Today, several groups work on hand transplantation with good results. The most relevant are found in Poland (15), France (16), Innsbruck (17) and Louisville (18).

Materials and methods

Patient selection and contraindications

The Baltimore group proposes the following inclusion criteria for the selection of candidates: age between 18 and 69 years, no coexisting medical conditions that may affect the outcome of the transplant (immunomodulatory, surgical or functional conditions), no psychiatric pathologies, no history of neoplasms in the last 10 years or HIV infection, and amputation for at least six months prior to the transplantation, with a good faith attempt to use prostheses and rehabilitation.

Moreover, for solid organ transplantation (SOT), additional criteria must be met (19,20). Inherited peripheral and inflammatory neuropathies, as well as neuropathies associated with systemic (diabetes, amyloidosis) and toxic diseases (metals and drugs) should be considered as relative contraindications for VAC, since transplantation requires post-transplant nerve regeneration, which could negatively affect the recovery of sensitivity or motor function in the hand (3,21).

In general, exclusion criteria to be considered include patients under 18 or over 69 years of age, and conditions that affect: a) the immunomodulatory protocol, such as chronic infections (HIV, hepatitis C), and preexisting immunological malignancies or deficiencies; b) surgical success and healing of coagulopathies, hematological diseases, vascular collagen disorders or connective tissue disorders; and c) functional results (healing of nerves or bones) in the presence of lipopolysaccharidosis, amyloidosis, metabolic diseases or bone genetic diseases. Other exclusion criteria are autoimmune inflammatory arthritis and extensive and severe osteoarthritis. In addition, patients may be excluded due to any other problem developed during the selection process (19,20). Similarly, the loss of the hand should be unilateral or bilateral and the level of amputation limited to the forearm.

Thereafter, a panel of screening tests is performed, including hematologic tests such as complete and differential blood count, reticulocyte count, platelet count, PT (prothrombin time), PTT (partial thromboplastin time), INR (international normalized ratio), ABO (for blood type compatibility; blood type A, B or O), Rh factor, major histocompatibility complex (MHC) and panel reactive antibodies (PRA).

Metabolic tests include serum electrolytes, renal function panel, creatinine, uroanalysis and liver function. Infectious tests involve cytomegalovirus detection, Epstein-Barr, herpes simplex, toxoplasmosis, varicella-zoster (IgG and IgM when indicated), HIV 1 and 2, hepatitis C, syphilis, hepatitis B and Mantoux skin test (TST). Cardiopulmonary tests involve electrocardiogram and echocardiogram or pulmonary function test with DL02.

Finally, radiology tests include abdomen ultrasound (to discard a tumor), hand and stump ultrasound, computerized axial tomography (CT), conventional angiography, functional magnetic resonance, paranasal sinus x-ray (to discard an infection or tumor), thoracic and simple bilateral hand x-ray, and wrist and forearm x-ray as indicated (19,20).

Diagnostic images (radiography, CT, NMR, among others) are important because they characterize the structural integrity of soft tissues and the bone of the receptor, which indicate how healthy a tissue is, and prevents anastomosis in a diseased or injured tissue. In addition, they describe structural damage (maceration of distal residual tissues, bone fragmentation, intra-articular fracture extension), either caused by amputation or by subsequent surgical procedures. This guides the surgical process, in the best possible way, where muscle mass and bone integrity need to be preserved. They also exclude any underlying disease that may compromise the function of the transplant or contraindicate life-long immunosuppression.

Angiography or angioresonance is used to identify the appropriate anastomotic vascular pedicle (radial or ulnar) for grafting. It is worth noting that ultrasound is useful for identifying signs of endothelial proliferation during postoperative surveillance, which would indicate graft rejection (22).

However, the assessment of coincident MHC is recommended, since the number of acute rejections seems to correlate with the

number of mismatched MHC, whose compatibility, according to one hypothesis, correlates with the development of antibodies in the donor. Therefore, this also influences the risk of developing graft vasculopathy in VAC (23,24).

Lastly, a multidisciplinary team should perform a complete clinical assessment of the candidates, including specialists (gastroenterologist, ophthalmologist, dentist, etc.) and psychological and social work support (19,20).

Immunology of the hand

Unlike solid organs (kidney, heart, liver, etc.), the hand is coated with skin, which has a very high antigenic load (25). In 2005, Tung *et al.* demonstrated that skin rejection is the first event in studies of limbs transplantation in mice (26), which coincides with findings in humans. The cellular components of the skin, associated with immune response, are keratinocytes, langerhans cells and dendritic cells. Keratinocytes produce proinflammatory cytokines that activate these cells in the dermis and epidermis, and chemokines that attract circulating lymphocytes into inflammatory foci and regulate the function of langerhans cells in the immune response (27).

On the other hand, Sugita *et al.*, when performing epidermal cell cultures, found that the expression of the major histocompatibility complex (MHC) class II in keratinocytes was promoted in this type of cells, while CD86 was expressed in langerhans cells. This finding allows identifying the role of keratinocytes in the appearance of antigens, through toll-like receptors, as well as their role in the regulation of the immune response (28). These results confirm that skin has the ability to trigger a large-scale immune response that can lead to skin rejection in hand allografts.

Immunosuppressive protocols

Induction therapy with both monoclonal (alemtuzumab/basiliximab) and polyclonal antibodies (ATG, that is, antithymocyte globulin) has been used since the Lyon transplant in 1998 based on the patient's immunological risk, and is followed by maintenance management, combined with mycophenolate mofetil (MMF), tacrolimus and steroids (25). In many studies, skin cell components have been characterized while searching alternatives to induce tolerance such as chimerism by transplantation of hematopoietic cells, together with cytokines of peripheral blood mononuclear cells in animal models, or reduction of pharmacological immunosuppression. This has yielded varying results, either transitory chimerism or risk of generating graft-versus-host disease (29-31).

Similarly, the experience of the Polish group, with six patients transplanted until 2011, reported the following scheme as a management protocol:

a) Induction: basiliximab, tacrolimus 5mg oral, MMF 2g oral, and methylprednisolone 1g intravenously.
b) Day 1: tacrolimus 5mg oral twice a day, MMF 1g oral twice a day, and methylprednisolone 500 mg intravenously.
c) Day 2: basiliximab intravenously, tacrolimus 5mg oral twice a day, and MMF 1g oral twice a day.
d) Days 3-7: tacrolimus (seru level 20 ng/mL), MMF 2g oral (daily), and methylprednisolone 500mg intravenously.
e) Maintenance: tacrolimus (peak level 10-15 ng/ml), 56 months after transplantation. Management was done with tacrolimus (peak level 10 ng/mL), steroids (5 mg / d), and MMF (2g/d) (15).

Until the report disclosed in 2011, the French group had performed five hand transplantations with ATG or alemtuzumab for the management of induction therapy, and tacrolimus, prednisone and MMF for maintenance (16). Despite the low number of patients, both protocols have shown favorable outcomes. Therefore, it is suggested that each center, according to its experience and the individual characteristics of each patient, creates its own protocols for immunosuppression (15-18,32-40).

Surgical procedure

As for the surgical procedure to implant the hand, bones, tendons, nerves and blood vessels of both the stump and the hand graft are identified. The order of the union is: fixation of the bones by means of plates and screws usually used in cases of arm fracture, anastomosis of arteries and veins, muscle and tendon repair, nerve repair, and skin closure. Cold ischemia time varies between 50 minutes and 12 hours (mean: 6 hours, 12 minutes) and depends, to a great extent, on the geographic distance between donor and recipient hospitals. (32,41,42).

Complications

Acute rejection

Globally, 85% of all hand transplant recipients have experienced at least one episode of rejection unrelated to induction or maintenance therapy (25) within the first year of transplantation. This is why it is considered as one of the main complications.

Rejection is identified by visual inspection and confirmed by skin biopsy, as it is a highly immunogenic tissue (43-46). Classical acute rejection is observed as an erythematous (diffuse or focal) maculopapular eruption, accompanied or not by edema and vesicles. Other clinical signs are desquamation, ulceration or necrosis (47,48). In addition, manifestations of atypical acute rejection affect the palmar skin and nails, so the lesion appears as a desquamative rash associated with dry skin, red papules and palmar thickening or lichenification, nail dystrophy, deformation or nail loss (47).

Treatment for acute rejection includes topical tacrolimus or clobetasol ointments, as well as systemic steroids and monoclonal antibodies as needed (49,50). The histopathological characterization of skin rejection is performed using the Banff classification (51,52). In the skin samples, an increase in the expression of adhesion molecules (Intercellular Adhesion Molecule 1 o ICAM-1, E-Selectin and P-Selectin) is evidenced in the vascular endothelium of the graft, which is associated with the severity of the rejection (25, 53). In addition, lymphocyte infiltrate is observed with predominance of T CD4+, CD8+, CD3+, and CD68+ lymphocytes, and Foxp3 transcription factor expression, which is also correlated with the severity of rejection (53-57).

Chronic rejection

Little is known about the risk of chronic rejection in humans, whereas hindlimb animal models with rats have shown thickening of the intima and light occlusion of the graft arteries at a histological level (47,58). In this model, repetitive episodes of acute rejection were induced and histological changes of chronic rejection were achieved, including loss of hair follicles and epithelium, and adnexial muscle atrophy, with macrophage infiltration and fibrosis.

Vascular alterations are late findings of rejection, suggesting that multiple episodes of acute rejection may lead to vasculopathy in the graft (47,59,60). Therefore, TH1 and TH2 have been proposed as immune activation pathways mediated by Helper TCD4+ T cells. The former is associated with acute rejection and is mediated by IFN-, TNF-α and IL-2 proinflammatory cytokines that increase immunogenicity in allografts. On the other hand, the TH2 pathway induces tolerance by means of IL-4,5,6 and IL-10 , which inhibit the production of IFN , and Th1 cells to suppress the production of IL-6 and TNF-α from monocytes. Nowadays, it is suggested that the TH2 pathway favors the production of alloantibodies, cytokines, and growth factors that induce the proliferation of TCD8+, cells, natural killer (NK) cells, B cells, macrophages, smooth muscle and endothelial cells that favor chronic rejection (61-63).

Pharmacological immunosuppression

Complications secondary to the immunosuppressive protocol, which prevent hand allograft rejection, may appear including infection, post-transplant diabetes, hypertension, nephrotoxicity, hyperlipidemia, leukopenia, cardiovascular disease, bilateral hip osteonecrosis, and increased risk of developing certain cancers (3).

Opportunistic infections

One of the most common is cytomegalovirus (CMV) infection, perhaps due to the high risk of latent virus transmission forms in leukocytes, epithelial cells and hematopoietic bone marrow stem cells found in the hand allograft (64). This may increase morbimortality in the recipient, as well as decreased graft survival and increased risk of acute rejection episodes (14,65-68). Negative CMV receptors may get infected through blood transfusions, community transmission and false CMV negatives in the donor. In addition, treatment with drugs such as Ganciclovir (GCV), Valganciclovir (ValGCV), Foscarnet and Cidofovir, alone or in combination, should be initiated, while monitoring is performed with polymerase chain reaction (PCR) for CMV (55).

Bonatti *et al.* (56), of the Innsbruck group, reported that their three hand receptors received antiviral prophylaxis with Ganciclovir (GCV) or Valganciclovir (valGCV) and still developed an infection by CMV. Two of them developed a complicated infection that required anti-CMV, hyperimmunoglobulin, cidofovir and foscarnet. In contrast, the third patient suffered from one type of non-invasive viremia by CMV. Furthermore, Ravindra *et al.* (69), of the Louisville group, reported that two of their three patients developed CMV infection; one of them went into remission with oral GCV, and the other was administered the same medication but intravenously, with complete remission.

Other infections reported in these patients were caused by human papilloma virus, herpes simplex, *Staphylococcus aureus, Clostridium difficile*, contagious molluscum, Pseudomonas sp., candida mycosis and *Alternaria alternata* (32,70,71). In general, it is necessary to contemplate the same considerations of solid organ transplantation, although there is no evidence regarding prophylaxis.

Neoplasms

Since hand transplantation patients have been monitored for less than 10 years, many of the side effects of long-term immunosuppression are still unknown, considering that, in general, they are healthy patients.

So, people undergoing solid organ transplantation are known to be at least three to five times more likely to develop neoplasms compared to the general population. The most frequent types of cancer are associated with virus and skin cancer (72,73), which is why it is essential to consider the risk of developing different types of neoplasms in patients with vascularized composite allograft (VCA), in particular hand transplantation. The risk of developing different types of neoplasms must also be considered. Landin *et al.* (74) reported basal cell carcinoma in a bilateral hand transplant recipient in 2006; the patient had received alemtuzumab and then combination therapy using tacrolimus, MMF and prednisone. 360 days after the transplantation, a nodular, rounded, pigmented and smooth lesion of 3 mm of diameter was found in the right nasal wing, which was removed without recurrence.

Kaufman *et al.* (18) reported the detection of mantle cell lymphoma in the third patient, who underwent hand transplantation by the Louisville group, and received alemtuzumab as an inducer, while tacrolimus and MMF were administered for maintenance.

Psychological aspects

The psychosocial factors in hand transplantation patients affect graft function and survival (75,76). This can be identified in the second hand transplantation in the world, which was performed in Lyon in 1998. This surgical procedure was successful although the patient did not adhere to the immunosuppressive management, nor to physical therapy; therefore, the patient required amputation of the graft in 2001 (14). This was related to the motivation and ability to incorporate transplantation experience in patients, which may lead to non-compliance with the pharmacological or rehabilitation regimen (77,78).

Some of the risk factors identified in psychological assessments in candidates for hand transplantation include social isolation, shame, decreased self-esteem, depressive coping style and poor quality of life (79). For this reason, it is important to conduct a detailed psychiatric interview in which transplantation is addressed, and to supplement it with psychological tests to assess body image adaptation and integrity, before and after the transplant (80-84). This is useful to perform the necessary therapeutic interventions, detect difficulties in the psychological integration process of the graft and, thus, obtain the best possible results in the long term.

Rehabilitation

Although part of the success of hand transplantation is attributed to surgical planning, it is not the only aspect to be taken into account to achieve a successful outcome (85). Rehabilitation programs are fundamental for the recovery of functionality in the transplanted hand, since a successful process requires patient commitment. It is also necessary to ensure that the patient will count on a team of experts that can provide guidance in terms of long-term recovery goals and expectations (86-91).

Before transplantation, therapists collect data on motion range, strength, stump sensitivity, and history of prosthesis use. They also find out if the patient feels pain, which is recorded by analogous verbal scale (48). As for the team of hand therapists, they should be responsible for the planning of therapy sessions, patient education and familiarization with information from transplant centers (32), which allows them to know the main complications and possible management. In addition, it is recommended to initiate therapy one week after surgery.

However, this therapy should be performed five days a week for an average of four hours a day for the first three months after transplantation (48), which requires commitment from the patient and the caregiver. Likewise, since the intensity in days and hours

varies among patients, they should be adjusted based on recovery in each case (90,91).

Research on the emotional aspects of these patients has focused on depression, anxiety, personality disorders and substance abuse, since they are the most frequent alterations, and are associated with functionality recovery expectations after the transplantation (92,93). With this is mind, the need to assess the degree of satisfaction and improvement of the quality of life of transplanted patients arises. These aspects are assessed through evaluation questionnaires that have not been standardized yet in all hand-transplantation programs (94-97). Such questionnaires include a) DASH (Disabilities of the Arm, Shoulder and Hand), which allows obtaining subjective and objective data from the patient, if a decrease of 15 points or more is found, a significant recovery in functionality is considered (98); b) Sollerman Hand Function Test, which incorporates tasks based on the patient's work and takes into account the quality of the grip patterns and strength to perform them (99,100); and c) The Carroll Upper Extremity Function Test, which evaluates the functional recovery of the graft (101).

Finally, the role of the caregiver is fundamental during the first post-transplantation phase, since patients, especially those receiving bilateral hand transplants, depend on someone else for daily living activities for weeks or months after the surgery. This is exacerbated by the physical fatigue caused by rehabilitation, immunosuppressive drugs and the emotional challenges of the demanding general program (48). Therefore, throughout the process, the family must be included to be provided with the necessary tools to meet this challenge in the best possible way.

State of the art

Information on the experience of each transplant center in the world is compiled by the International Registry of Hand and Composite Tissue Transplantation (IRHCTT), where reports are delivered voluntarily (non-mandatory). In total, 89 hand transplantations were performed between 1998 and 2010 (102). The last report was published in 2010 and provides data on the follow-up of 49 hand transplantations in 33 patients (18 bilateral and 17 unilateral). Follow-up was performed on 31 patients for minimum one year; the age range was 19 to 54 years, with a mean age of 32 years. Regarding sex, 31 patients were males. Finally, in relation to the transplantation itself, wrist (46%), distal forearm (19%), middle forearm (17%), proximal forearm (14%) and elbow (4%) were the most common.

As a result, 30 patients regained tactile and discriminative sensitivity. Motor recovery was initiated in the extrinsic muscles (gross motor), and then in the intrinsic muscles of the hand, for 9 to 15 months, in most transplanted patients (32). This motor return depends on the anatomical level of the transplant (distal is better than proximal), and on the postoperative rehabilitation regimen; sensory feedback is conditioned to the regeneration of the nerve (47). Quality of life improved in 75% of patients, which enabled them to resume their work activities. Moreover, the systematic review by Landin *et al.* found that the score decreased by an average of 27.6±19.04 points, through a disability comparison with the DASH survey, before and after the transplantation. Significant functional gains of the transplanted limb were also evidenced (103).

The main complications associated with transplantation are (32): a) opportunistic infections by CMV and herpes (29 cases); b) limited cutaneous necrosis (6 cases); c) permanent hyperglycemia (3 cases); d) arterial thrombosis (1 case); f) arteriovenous fistulae (1 case); g) end-stage kidney disease (1 case) that required hemodialysis 8 years after hand transplantation; h) transplant loss (1 case) due to poor adherence to treatment (29 months post-transplant), with conscious patient decision to suspend immunosuppression; i) intimal hyperplasia at day 245 post-transplant (1 case); j) bilateral transplantation involving bacterial infection (day 45 post-transplant), and k) bilateral hand and face transplantation, which resulted in death by cerebral anoxia (day 65 post-transplant).

However, IRHCTT does not take into account the cases reported by the Chinese groups, including Pei *et al.* (104), who reported 15 hand transplantations performed in 12 patients between 1999 and 2008, with a mean age of 34 years (19-52 years). Seven of these patients lost the grafts due to lack of adherence to the treatment. Overall, the results were poor, compared to transplantations performed in other centers around the world.

When comparing unilateral and bilateral transplantation with DASH scores, better functional results were observed in bilateral transplants. Even so, the results were positive for both groups from an overall perspective, which implies independence and return to the patients' work activities (105,106).

Future of hand transplantation

Despite advances in immunosuppressive management and rehabilitation programs, there are still limitations, such as nerve regeneration of the transplanted hand, which occurs both at the distal and proximal levels. The case of proximal segment amputations is more relevant due to the difficulty of adapting to the prosthesis, which is why the transplant is required. Nevertheless, new research is expected to develop strategies to improve this aspect (3,107).

Immunosuppressive protocols are another important factor in hand transplantation, since there would be no graft survival without them. Currently, no protocols develop immunocompetence in the transplanted patient to avoid immunosuppression. Thus, these strategies are expected to be established in the future, to prevent the side effects of pharmacological immunosuppression.

It should be noted that protocols that include transient or sustained chimerism have already been developed; however, in this case a living donor is needed, which is not possible in hand transplantation (108).

Today, research on autotransfusion protocols and mesenchymal stem cells that regulate the possible decline of the immune response can be found, even if its use is limited to experimental studies. Although the use of mesenchymal bone marrow cells has shown to generate stable chimerism and prolong transplant survival in animal models, it has not yet been tested in humans (109,110).

Another modality under study is based on the use of bioreactors to prolong ex vivo, that is, outside the donor and the recipient, in an alternate environment, to extend the survival of the graft and to modulate its immunogenicity so as to improve the function of the graft (111).

It has also been mentioned that patients undergoing hand transplantation have a history of difficulty to adapt to prostheses, despite their interest and the interventions made by specialists to achieve this goal. This entailed high rejection rates of these devices (112,113). The options offered to patients with amputations of upper limbs have changed and expanded in order to cover the physical demands of potential candidates.

At present, advances have been made in prostheses adaptation and management, such as the case of selective muscular reinnervation in proximal amputation cases, which has allowed to develop the perception and position of the amputated segment. This technique consists of using non-functional muscles as amplifiers of the non-functional nerves and, thus, extending the nerve cover as distal as possible, approaching the distal end of the prosthesis (115,116).

However, the main causes of prostheses abandonment include adaptation difficulties, lack of participation in the selection of the prosthesis, functionality, patient expectations and education on the proper use of the prosthesis. Thus, people who participate in the selection of devices are more successful in adherence to their everyday use. (117).

In addition, there are six options in the market for the patients with upper limb amputation: not using a prosthesis, using passive prosthesis, body propulsion, electric propulsion, hybrid propulsion or specific activity propulsion. Choices must be made with the patient, so that proper assessment and advice can be provided for a correct selection (118). Because the devices do not fulfill all the activities of daily life, and to be able to respond to the demands of the users and their profession, it is necessary to use more than one device. To be successful and to meet patient expectations, their opinion on the process is essential (119,120).

Finally, hand transplantation and prosthesis adaptation should not be seen as mutually exclusive, but as treatment options that differ from the risk and benefit profile for the patient, and from their ethical, clinical, aesthetic and functional implications (121).

Conclusions

Hand transplantation, rather than a composite tissue transplant, should be considered as an organ transplant that depends on the comprehensive management by a multidisciplinary team, which requires a support network and motivation from the patient, along with compliance with pharmacological management.

When rejection occurs, it should be classified in order to determine the treatment. In consequence, a skin biopsy is considered as the gold standard for diagnosing acute rejection, although its role in chronic rejection should be questioned, since it can generate false negatives according to the depth of the sample.

Also, rehabilitation is a vital process to recover the functionality of the hand, as well as psychological accompaniment to prevent graft loss due to lack of adherence to the treatment.

Finally, new research is expected to create strategies to develop tolerance and thereby reduce management through immunosuppression. In addition, the pros and cons of hand transplantation, the experience of the transplant group, the side effects of short- and long-term drugs, and the possible complications associated with immunosuppression in each of the hand VAC cases should always be evaluated.

To see the management algorithm, please refer to Annex 1.

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Annex 1. Hand transplantation flow chart.