

International vascularised composite allotransplantation activity: implications for Australia

Although hand transplantation has the potential to transform lives, the procedure is not without risk

March 2018 heralded 7 years since the only Australian to date received a hand transplant. The recipient has physically and psychologically integrated the transplanted hand and reports significantly improved quality of life;¹ motor and sensory functions continue to improve incrementally with ongoing hand therapy. The Transplantation Society of Australia and New Zealand (TSANZ) Vascular Composite Allograft (VCA) Advisory Committee met during the TSANZ annual scientific meeting held in Melbourne in April 2018. Transplant physicians and surgeons and reconstructive microsurgeons comprise the advisory committee, with scope to co-opt expert members (eg, in bioethics) as required. Despite the success of the seminal hand transplant in Australia, no further patients have progressed to the transplant waiting list. In light of this, the Advisory Committee reflects in this article on the status of hand transplantation internationally and considers its relevance for Australia.

VCA refers to the transplantation of multiple tissues, including muscle, bone, nerve and skin, and a functional unit, such as a hand, from a deceased donor to a recipient. Although hand transplantation is the most common form of VCA,² there is an increasing number of other VCAs being performed internationally, which include face, larynx and tracheal, abdominal wall, lower limb, uterine and penile transplantation.

Since the first Australian hand transplant procedure, clinical guidelines under the governance of the TSANZ have been established for VCA, specifically with reference to transplantation of hands. Despite many similarities with other solid organ transplantations, hand transplantation is unique on a number of fronts. Unlike other solid organ transplants, hand transplantation is not a life-saving procedure; rather, it is performed to improve the quality of life. It must be made clear to potential recipients that immunosuppression-related complications may in fact reduce life expectancy. In contrast to other solid organ transplants, a hand transplant is visible and may have an impact on body image.³ As with all transplants, success hinges on control of the immune response and adherence to immunosuppression; non-adherence will result in graft rejection, necessitating graft removal.⁴ In addition, and different from other solid organ transplant recipients, hand transplant recipients are required to partake in lengthy, intensive and ongoing rehabilitation to achieve useful hand function.

Many of the inclusion and exclusion criteria for consideration for hand transplantation share commonality with other solid organ transplants. One salient point of difference is that the potential recipient must have sustained bilateral limb loss. This is not the case worldwide and, indeed, the longest surviving recipient received a unilateral hand transplant in the presence of a functional contralateral hand. The position of the TSANZ is based on the level of disability of a unilateral amputee and, thus, the potential gain with transplantation versus the risks of adverse events. The data show that unilateral amputees with one remaining healthy hand, which assumes dominance, can usually perform up to 90% of activities of daily living.⁵ These data also affect bilateral amputees, as not all bilateral upper limb amputees will receive bilateral upper limb transplants. The level of each amputation requires assessment, as this will influence the functional success of the transplant as motor and sensory recovery is dependent on the recipient's nerve fibres to reinnervate the donor's hand. The more proximal the amputation, the longer it takes for reinnervation and gain of function. Furthermore, individuals with proximal neuromuscular dysfunction are currently excluded from transplantation in Australia and New Zealand.

A criterion that requires further discussion before inclusion in local protocols is the requirement that the patient has tried and failed with the use of prosthetics. The sophistication of current prostheses yields excellent results. Indeed, no differences in the measures of motor function were detected when comparing seven hand transplant recipients with seven individuals using prostheses. However, the psychosocial outcomes of quality of life assessment (using the validated 36-item short form health [SF-36] questionnaire) revealed that transplant recipients scored higher than prosthetic wearers in four out of eight areas, which included "role physical", "vitality", "role emotional" and "mental health", and were at average levels for an age-matched male population. Comparable scores between transplant recipients and prosthetic wearers were obtained in other scales such as "physical functioning", "bodily pain", "general health" and "social functioning".⁶ Thus, although myoelectric prostheses have increasingly advanced ergonomic and functional features, these data demonstrate that the immense sensory capacity of the hand cannot be recapitulated. The counterargument is that the use of prostheses obviates the need for immunosuppression and prolonged rehabilitation. At present, the TSANZ VCA Advisory Committee

Karen M Dwyer¹

James D Burt²

Tim Bennett²

¹ Deakin University,
Geelong, VIC.

² St Vincent's
Hospital Melbourne,
Melbourne, VIC.

karen.dwyer@
deakin.edu.au

encourages an assessment by a prosthetic team and a trial of a prosthesis before hand transplantation.

With the passage of time, a greater understanding of the immunological challenges facing hand transplant recipients has evolved. As with solid organ transplantation, hand transplant recipients are vulnerable to all forms of rejection, including cell-mediated,⁷ antibody (human leucocyte antigen [HLA]-⁸ and non-HLA-mediated⁹) and chronic rejection.¹⁰ The current immunosuppressive regimens employed are based on those used in solid organ transplantation, and include induction therapy at the time of transplantation followed by triple drug maintenance therapy. Therefore, not surprisingly, the complications of immunosuppression experienced by hand transplant recipients mimic those of other solid organ recipients, particularly with respect to metabolic complications (such as post-transplant diabetes), malignancy and infection.⁷ A decline in kidney function, which was most marked in the first year after transplantation, has recently been reported in hand and face VCA recipients.¹¹ Interestingly, cardiovascular disease after VCA has not yet been reported — which may reflect the make-up of the recipients, who, on average, are young (median age, 32.5 years; range, 17–67 years) — and in many patients, the amputation was a result of a working injury rather than due to a comorbid disease.⁷ We may, however, see a subsequent reporting of cardiovascular disease given its well established association with renal dysfunction.

Mortality is an important consideration, as hand transplantation is a non-life saving procedure. Taking into account the combined experience from western Europe, Australia and the United States, the mortality rate for hand transplant recipients is 0% (50 patients undergoing isolated unilateral or bilateral upper limb transplantation), with a graft survival rate of 90.5% per limb transplanted (seven out of 74 limbs transplanted were lost acutely or chronically).² These data exclude those patients who received a transplantation in China and experience high graft loss due to cost limiting the access to immunosuppression,¹² and recipients of multisite (hand and face, hand and leg) transplants, which have been associated with a high mortality. Together, these recipients account for 62.5% of all known graft losses.²

In Australia, there are over 35 000 amputees, the majority of whom (75%) have had lower limb amputations — most often as a consequence of diabetes and vascular disease.¹³ Even though there are about 8500 upper limb amputees, only one person has proceeded to transplantation in Australia, with only a few others being actively assessed. There are many reasons that underpin this discrepancy, which may include lack of awareness of and access to the procedure (the sole case has been performed in Melbourne), the functional utility of prostheses,

and the lack of benefit for unilateral amputees, together with potential complications arising from immunosuppression.

Face transplantation is an emerging therapy, with about 40 face transplants performed worldwide for devastating facial defects.¹⁴ In Australia, there is interest in this technique, although detailed protocols are yet to be established. Face trauma results in significant disfigurement; however, function of the face (to breathe, eat, smell and speak) is also often compromised. Whereas the functional outcomes of hand transplant are collated in an international registry⁷ and reported,² outcomes from face transplant are variable and have only been reported in a minority of patients. Graft loss has been reported after face transplantation as has patient death.¹⁴ A 2017 systematic review found that quality of life outcomes have been reported in only 14 face transplant recipients.¹⁵ The results from this systematic review demonstrated that, overall, there is improvement in quality of life, but the authors rightly acknowledged the paucity of available data in addition to the significant heterogeneity of reporting.¹⁵ The TSANZ VCA Advisory Committee would like to see greater reporting of outcomes after face transplantation before its application in the Australian setting.

For some patients, hand transplantation is a safe and viable therapy after upper limb amputation. Although life enhancing, the risks of complications due to immunosuppression are real, and all patients must be counselled that graft loss and death may occur. Such risks and benefits should be considered in the context of the increasing sophistication of prostheses, which yield excellent functional outcomes; thus, a considered recipient selection is critical. The TSANZ VCA Advisory Committee continues to endorse hand transplantation as a potential therapy for bilateral physical or functional amputees. At this time, multisite transplants (face and upper limb, lower and upper limbs) are ill-advised due to the excess morbidity and mortality, and the role of face transplantation in the Australian context is as yet not defined. A limited number of other VCAs have been performed worldwide. At present, the TSANZ VCA Advisory Committee considers these therapies as experimental, and it will require a multidisciplinary ethical, biological and psychosocial discussion before they are performed in Australia.

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