



History and ethics of hand transplants

Michael Errico¹ • Neil H Metcalfe¹ • Alastair Platt²

¹Hull York Medical School, York, Hull HU6 7RX, UK

²Castle Hill Hospital, Hull HU6 7RX, UK

Correspondence to: Michael Errico Email: hy8me@hyms.ac.uk

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Summary

Hand transplantation is a form of composite tissue allotransplantation, whereby the hand of a cadaveric donor is transferred to the forearm of an amputee. The aim of such a procedure is to achieve better outcomes in terms of functionality and appearance when compared with prosthetics. The microsurgical techniques required have been well established for many years. In addition, advances in immunosuppressive therapy have meant that hand transplantation is a feasible therapeutic option. However this is not a life-saving procedure, requiring lifelong antirejection treatment with potentially serious side-effects. Hand transplantation is therefore a controversial concept with ethical, financial and psychological implications that need careful consideration. Before this treatment can be fully accepted, further research is still required; this should be directed towards achieving immunological tolerance, while minimizing costs and potential side-effects of post-transplant therapy.

Introduction

Hands are composed of complex structures, which enable extraordinary dexterity and fine tactility. Extensive use of our hands during occupational and domestic tasks makes them especially vulnerable to hand trauma. In the UK, 20% of accident and emergency admissions present with hand injuries.¹ Some of the most devastating injuries can leave the patient with functional impairment and have profound psychological implications.² When dealing with serious hand injuries, surgeons aim to fulfil the basic tenets of plastic surgery: the restoration of form and function. In the case of traumatic amputation, the limb may be replanted in its original position. However, due to the mutilating nature of certain injuries,

this may not always be possible, making hand prosthetics the only surgical option.

Methods

The initial literature search was made through Ovid MEDLINE[®] and PubMed, using the search terms 'Hand Transplantation' and 'Composite Tissue Allotransplantation.' Relevant reviews were hand searched and their reference lists were checked for suitable papers; this was also performed on all selected articles. The 'International Registry on Hand and Composite Tissue Transplantation' website was used to assess the total number of hand transplants performed worldwide; this was a preliminary search later

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confirmed by contacting coordinators of the website. NICE guidance was used as a reference tool for the most recent evidence based clinical practice. Newspaper articles and websites reporting recent updates in the field were accessed via standard Internet search engines.

Major advances in microsurgery and immunosuppressive agents have in recent years meant that hand transplantation is a realistic possibility for some. This is a surgical procedure wherein a hand from a cadaveric donor is given to a recipient. The main aim of this procedure is to provide a hand that not only looks more natural than prosthesis, but also allows for motor control, and sensation.³ As with other forms of transplantation, this exciting advance in modern surgery has met with controversy. This article reviews the history of hand transplantation, and addresses some of the issues surrounding its development.

The history of hand transplants

Hand transplantation is a surgical procedure that has evolved from close collaborations between reconstructive and transplant surgeons.⁴ Technically, the procedure is similar to hand replantation,⁵ and the microsurgical techniques required have been well established for many years. However, it expands on some of the immunoregulatory challenges experienced with solid organ transplantation. Unlike single organ transplants, a hand transplant is a composite tissue allotransplantation (CTA) consisting of skin, muscle, tendons, bone, cartilage, fat, nerves and blood vessels. Each individual tissue possesses a different degree of antigenicity; skin, being the most antigenic organ in the human body,^{6,7} elicits a strong immune response when recognized as foreign tissue. It was therefore believed that the only way to prevent acute rejection of a hand graft would be to immunosuppress the patient to such an extent that the resulting complications would outweigh the benefits of the operation.⁶

A team of surgeons in Ecuador performed the first documented attempt at hand transplantation in 1964.⁵ During this time, immunosuppressive treatment was in its infancy; a regimen of prednisone and azathioprine was not sufficient to prevent irreversible acute rejection within two weeks of the procedure.⁵ At the time, leaders in the field of transplant surgery, believed that

overcoming the immunogenicity of a CTA was an unattainable prospect.⁷

Although the development of CTA seemed to have reached a standstill, the next three decades saw major advances in solid organ transplantation.⁵ These improvements coincided with the development of enhanced immunosuppressive drugs including calcineurin inhibitors, such as cyclosporine A and tacrolimus, and the antimetabolite, mycophenolate mofetil.⁵ With a better arsenal of drug therapy at their disposal, researchers reignited their interests in CTA. They used animal models such as rat hind limb allografts to attempt to overcome the immunological barriers inherent to CTA. By the 1980s, Black *et al.*²⁹ were able to demonstrate long-term survival of limb transplantation using low-dose cyclosporine.⁸ These results showed for the first time that CTA was a future clinical possibility.

In September 1998, the first human hand transplant was performed by a team of surgeons in Lyons, France.⁹ The team, led by Jean-Michel Dubernard (1941–present), transplanted the right forearm of a brain-dead donor to a male recipient (Clint Hallam, 48) with a traumatic mid-forearm amputation.⁹ This procedure lasted just over 13 h; however, its initial success would only be short lived.¹⁰ The patient was not able to adapt psychologically to the assimilation of an unfamiliar hand. He eventually stopped following his postoperative immunosuppressive regimen, resulting in acute tissue rejection. In 2001 he eventually required surgical amputation of the graft.¹⁰

Within a year, the Louiseville Hand Transplant Team in the USA achieved long-term hand graft survival.¹¹ Their work was central to the subsequent success seen in hand transplant centres around the world. Where progress in the field of CTA had previously been slow and protracted, rapid advances were beginning to be seen. The first ever double hand transplant was performed in Lyons in January 2000, as manipulation of the immune response became more refined using conventional immunosuppression.^{12,13} This paved the way for other forms of CTAs to be used, and face transplantation soon became a reality.

In May 2002, Dubernard founded the International Registry on Hand and Composite Tissue Transplantation (IRHCTT).¹⁴ This aimed to advance the science of CTA by combining clinical

experience from around the world and making it easily accessible to transplant specialists in the international community. In 2008 and 2010 the IRHCTT published outcome data based on all the cases that have been submitted to the registry.¹⁵ The records of 33 patients who had received unilateral or bilateral hand transplants since 1998 were analysed.¹⁵ Although acute rejection episodes occurred in 85% of subjects within the first year,¹⁴ these were all successfully managed by altering the postoperative immunosuppressive regimen. In fact, current long-term graft survival was found to be 94% and graft failure was solely due to non-compliance with immunosuppressive medication.^{14–16} Therefore, despite the heterogeneity of foreign antigens associated with CTA, current immunosuppressive protocols have proved to be effective in preventing rejection in patients with hand transplants.

In addition, the IRHCTT reported encouraging functional outcomes; 100% of patients recovered protective sensation, 90% of patients developed tactile sensation, while 82.3% also recovered discriminative sensation.¹⁵ Hand movement was achieved in all patients, enabling them to perform most daily activities including eating, grasping objects and shaving.¹⁵ These factors have enabled many of these patients to return to work following surgery.^{14,15}

Debate

As advances in medicine make hand transplantation a realistic clinical option, ethical considerations surrounding this procedure should not be overlooked. Critics may argue that the risks associated with hand transplantation outweigh the potential benefits.¹⁷ The lifelong immunosuppressive protocols required down-regulate the host's immunity in a non-specific manner, which could inadvertently put patients at risk of developing potentially fatal conditions.¹⁰ The IRHCTT study showed that opportunistic infections, such as cytomegalovirus reactivation, clostridium and herpetic infections were reported in 87% of subjects; metabolic complications such as hyperglycaemia, hyperlipidaemia and impaired renal function occurred in 52% of subjects.^{3,15} Of note, however, no life-threatening complications or malignancies have been reported, although these do remain theoretical possibilities.¹⁴ Nevertheless, hand

transplant surgery is 'non-essential' surgery, which is life-enhancing rather than life-saving. The alternative is hand prosthetics, which carries a significantly reduced side-effect profile. In view of the bioethical principle of non-maleficence, justifying the risks of such a procedure when other safer options exist remains an overriding concern. Not allowing such a procedure may therefore be seen as acting in the patient's best interest. It is also true, however, that there is no moral justification in negating a feasible clinical option based on a physician's paternalistic idea on what would be best for a patient. It is up to the patient to weigh up the risks and benefits of a procedure, and based on their choice, their autonomy should be respected.

In a time where healthcare expenditure is high on the public agenda, financial implications of performing non-life-saving procedures also need consideration. The lifetime cost of a single hand transplantation is approximately \$528,293; on average 62% of this total is due to expensive immunosuppressive therapy and postoperative management.¹⁸ The lifetime cost for a single prosthetic adaptation is approximately \$20,653;¹⁸ a much more cost-effective option in the long run. The economic burden in patients requiring solid organ transplants is also significant. It has been estimated that over \$30,000 is spent in the first year after transplantation and approximately \$15,000 is spent every year after that.¹⁹ These costs, however, are warranted for patients requiring liver or kidney transplants, as they are life-saving procedures. Hand transplants are not essential for life, and recent data taken from the IRHCTT have shown that hand transplantation for single arm amputees is not an effective option.¹⁸ The quality-adjusted life years (QALYs) of prosthetic adaptation exceed those for hand transplantation, due to the complications of immunosuppression.¹⁸ Furthermore, only limited information on the longevity of the treatment is available, as successful hand transplants are little more than 10 years old.²⁰ It is therefore difficult to justify burdening an already stretched National Health Service with such expensive treatment, the long-term outcomes of which are not guaranteed.

Quality of life is a subjective concept that incorporates the notion of physical wellbeing and mental health. Studying effectiveness in terms of QALYs is useful for population studies, but does

not take in to account an individual's response to treatment. The loss of a hand is a catastrophic life event, and dealing with the consequences may be extremely challenging. Reaction to such a loss will inevitably differ from person to person, but the psychological impact of severe hand injuries is well documented.² People with amputated hands can develop grief and bereavement reactions, emotions that are notoriously difficult to overcome. Although prostheses are designed to restore an element of functionality and appearance, even the most technically advanced could never compensate for a lost hand. Matthew Scott, a New Jersey paramedic who received a hand transplant, expressed his sense of loss and deprivation at not being able to hold his family, something his hand transplant helped to correct.²¹ Hand transplantation is an alternative for individuals unable to overcome the functional and emotional consequences of amputation with a prostheses. It is clearly beneficial in certain individuals and taking away this option could have serious repercussions to the patient's long-term emotional wellbeing.

When deciding who is eligible for a hand transplant, its psychological impact is an issue that is not ignored. A hand transplant is a visible entity taken from a deceased donor and needs to be incorporated into the patient's sense of self.¹⁶ Failure of the first hand transplant followed poor integration of the transplanted hand in to the patient's own body image. It could be argued that this was a direct consequence of suboptimal patient preparation and inadequate expectations. Accepting a foreign hand as an individual's own requires long-term psychological resilience. Transplant recipients are therefore carefully selected through clinical and psychiatric screening; individual risks and benefits are assessed, and recommendations are made to optimize the patient's standing for treatment. Following the procedure, ongoing support is required, focusing on physical and psychological rehabilitation. This continuum of care is also provided for patients receiving hand prostheses, albeit with far fewer resource implications seen in hand transplantation. It would therefore seem more acceptable to focus efforts on maximizing the patient's psychological support following amputation, bypassing the need for such radical treatment.

Patients deciding on hand transplant surgery need to make their decision based on potential risks, benefits and burdens of such a procedure. To do this, it is important that the treating physician offers specialist knowledge, experience and clinical judgement in a non-influential manner. The experimental nature of this treatment however casts doubt on how informed a patient's decision can truly be. Our experience in the field is only based on a small data-set collected over a period of 11 years. The true impact of long-term sequelae is not fully understood, and this uncertainty could potentially influence the individual's decision-making process. In addition, the benefits of such a procedure could be unintentionally exaggerated by an overzealous physician, motivated by the thrill of medical advancement.²¹

Where are we now?

To date, the IRHCTT have received details of 51 separate hand transplantations, performed in centres from 12 different countries around the world (Table 1). However this procedure is yet to be performed in the UK. National Institute for Health and Clinical Excellence guidelines currently state that there is simply not enough evidence on the safety and efficacy of hand allotransplantation to draw any firm conclusions.²³ To perform this operation, NICE recommends that special arrangements for clinical governance, consent and research are to be made.²³ Any data obtained should subsequently be submitted to the IRHCTT and transplant UK, so that safety of the procedure can be evaluated further.²³ This would add to a body of evidence that would help to make a more informed decision on the applicability of such a procedure for future amputees. Leeds General Infirmary have recently announced they are actively seeking suitable candidates to undergo this procedure.²⁴ The team led by Professor Simon Kay, aim to perform this operation by 2012, making it the country's first attempt at hand transplantation.²⁴ Similarly, Professor Peter Butler of the Royal Free Hospital in London, is seeking patients to perform the UK's first simultaneous hand and face transplant.²⁵ This procedure has only ever been carried out once in 2009 by surgeons in France; they performed a partial face and double

Table 1
Total number of unilateral and bilateral hand transplants submitted to the International Registry on Hand and Composite Tissue Transplantation.²²

Year	Unilateral		Bilateral	
	Centre	No.	Centre	No.
1998	Lyon, France	1		
1999	Louisville, USA	1		
	Guangzhou, China	2		
2000	Nanning, China	4	Lyon, France	1
	Kuala-Lumpur, Malaysia	1	Innsbruck, Austria	1
	Milan, Italy	1	Guangzhou, China	1
2001	Louisville, USA	1	Harbin, China	1
	Milan, Italy	1		
2002	Brussels, Belgium	1	Harbin, China	1
	Harbin, China	1		
	Nanjing, China	1		
	Milan, Italy	1		
2003			Innsbruck, Austria	1
			Lyon, France	1
2006	Wroclaw, Poland	1	Innsbruck, Austria	1
	Louisville, USA	1	Valencia, Spain	1
2007			Lyon, France	1
			Valencia, Spain	1
2008	Wroclaw, Poland	1	Munich, Germany	1
	Louisville, USA	2		
2009	Pittsburg, USA	1	Paris, France	1
	Wroclaw, Poland	2	Lyon, France	1
2010	Pittsburg, USA	1	Pittsburg, USA	1
	San Antonio, USA	1	Pittsburg, USA	2
	Wroclaw, Poland	1	Louisville, USA	1
			Wroclaw, Poland	1
2011	Los Angeles, USA	1	Mexico city, Mexico	1
	Atlanta, USA	1	Melbourne, Australia	1
	Wroclaw, Poland	1		
Total		30		21

hand transplant on a burn victim, who eventually died two months later following a heart attack.²⁵

The future

The holy grail of transplantation surgery is for the host to achieve graft tolerance, which would negate the need for immunosuppression.⁸ This possibility has already been recognized in animal models through the phenomenon of chimerism, which is the co-existence of donor and recipient cells in the host organism.²⁶ Theoretically, a state of tolerance can be achieved by simultaneously incorporating elements of the donor's immune system and the graft itself.⁵

This may be accomplished by providing donor pluripotent haematopoietic stem cells, which would re-programme the immune system of the recipient and eliminate alloreactive leukocytes.^{5,6,8}

Although this is an attractive concept, the reality is more complicated. While chimerism is one of the oldest studied approaches to induce tolerance,⁶ its clinical application has been impeded by severe toxic side-effects inherent to bone marrow transplantation protocols.^{27,28} Prior to the injection of allogenic bone marrow cells, conditioning regimens include lethal whole body irradiation or total lymphoid irradiation.²⁸ To induce tolerance like this in clinical practice would require feasible conditioning protocols, which carry minimal risk to the patient. Before this can be achieved, many more years of active clinical research are required.

Conclusion

Hand transplantation has come a long way since 1964. The capability of preventing allograft rejection while achieving good functional recovery means that it is already a feasible treatment modality. However, the cost of such a procedure in addition to a lifelong commitment to potentially harmful medication makes it a difficult option to justify on an already strained healthcare system. Although the immune system can now be manipulated to good effect, the major obstacle in this field still surrounds the issue of immunity. If tolerance could be achieved in the future, this could minimize costs and potential side-effects of post-transplant therapy. Accomplishing this, hand transplantation may transform from an experimental procedure to standard practice, as seen with solid organ transplantation.

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