NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of hand allotransplantation

Hand transplantation

Individuals whose hands have been severely damaged by injury or disease may undergo amputation.

This procedure involves transplanting a hand from a recently deceased donor to the amputated stump. The donor bones are rigidly fixed to those of the patient and the blood vessels, nerves, tendons and skin are restored.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in August 2010.

Procedure name

- Hand allotransplantation

Specialty societies

- British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS)
- British Orthopaedic Association.
- British Society for Surgery of the Hand
- British Transplantation Society

Description

Indications and current treatment

Amputation is the removal of a body extremity by trauma or surgery. It is used to control pain or a disease process in the affected limb. The level of arm amputation can vary from the wrist to the proximal forearm. Common treatment options following amputation include the fitting of a prosthesis to restore hand function, or where possible, surgical reimplantation of the hand.

What the procedure involves

The aims of this procedure are to provide a hand that is more natural than a mechanical prosthesis, and to improve function.

Before the procedure candidates are required to undergo careful psychological assessment of their motivation and likely compliance with postoperative rehabilitation and immunosuppressive medication. A cadaveric limb, with basic matching factors of sex, size and appearance, is surgically removed below the elbow to conserve vital structures. Genetic matching is routinely practiced but is not always the first consideration when selecting a donor hand.

Hand allotransplantation is carried out with the patient under general anaesthesia, which may be supplemented by a regional nerve block. A tourniquet may be used for haemostasis. The radius and ulna from the donor limb are fixed to those of the recipient using intramedullary pins or plates. Arteries and veins are anastomosed using standard techniques. The major nerves are repaired and others are joined if possible. Tendons are repaired either individually or in groups.

Following the procedure the limb may be immobilised in a plaster splint for a number of weeks. The patient should undergo intensive rehabilitation including physiotherapy, occupational therapy and possibly electrostimulation for best restoration of function. Long-term immunosuppression is needed to reduce the possibility of rejection.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to hand allotransplantation. Searches were conducted of the following databases, covering the period from their commencement to 16 July 2010 and updated to 25 October 2010: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during

consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with hand amputation.
Intervention/test	Hand allotransplantation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on approximately 33 patients from 1 case series[1] and 2 case reports[2,3].

Table 2 Summary of key efficacy and safety findings on hand allotransplantation

Abbreviations used: HLA, human leukocyte antigen.

Study details	Key efficacy findings	Key safety findings	Comments
Petruzzo P (2008)[1] International registry **Case series** International Recruitment period: 1998 to 2007 Study population: Patients having previously undergone hand amputation. Median time since amputation = 4 years. Level of amputation: wrist 50%, distal forearm 27%, Mid forearm 20%, proximal forearm 3%. n = **30 (38 hands)** Age: 34 years (median) Sex: 93% male Patient selection criteria: not reported Technique: Donor selection based on race, gender, size and skin colour matching, HLA matching, and negative lymphocytotoxic cross-matching. Hand harvested from heart-beating donors in 68% of cases. Median cold ischaemia time 6 hours. The repair sequence of different tissues varied considerably but in 81% of hands bone fixation and arterial / venous anastamoses was performed first, followed by suturing of nerves and tendons. Two arteries and a variable number of veins anastamosed. Median and ulnar nerves repaired in all cases. Physiotherapy and electrostimulation during rehabilitation. Majority of patients received polyclonal antibodies, and all were given broad-spectrum	Number of patients analysed: **29 patients, 37 hands** **Quality of life** More than 70% of patients reported improved quality of life, with most patients returning to work. **Graft survival** Graft survival was 100% at 1- and 2-year follow-up. Graft loss occurred in 10 hands transplanted at Chinese centres, all due to non-compliance with immunosuppression regimen. Acute rejection episodes occurred in 85% of patients within the first year. 7% of patients suffered 5 episodes in the first year. Rejection episodes were reversible in all compliant patients when promptly reported and treated. **Hand function** 90% of patients developed tactile sensibility, and 72% developed discriminative sensibility. Extrinsic muscle function recovery allowed all patients to grasp and pinch. Intrinsic muscle recovery occurred later (at 9 to 15 months post transplantation) to enable patients to perform most daily activities. Function was assessed using the hand transplantation score system, using 6 factors: Appearance (15 points), sensibility (20 points), motility (20 points), psychological and social acceptance (15 points), daily activities / work status (15 points), and patient satisfaction / general wellbeing (15 points). Maximum score (best outcome) of 100 points Group mean scores (points) – unilateral left hand Transplantation date: 2001 / 1999 Follow up: 5 years / 7 years Appearance: 8.5 / 15 Sensibility: 8 / 15.5 Movement: 12 / 15.5 Psychological: 15 / 14 Daily activities: 5 / 13 Satisfaction: 1 / 13	**Complications** Complications successfully treated with additional surgery Early post-operative skin necrosis: 10.8% (4/37) Arterial thrombosis: 2.7% (1/37) Venous thrombosis: 2.7% (1/37) Multiple arteriovenous fistulae: 2.7% (1/37) Complications related to immunosuppression. Most were transient and reversible Serum sickness: 3.4% (1/29) Opportunistic infection: 65.5% (19/29) Cytomegalovirus reactivation: 27.6% (8/29) Herpes virus infection: 6.9% (2/29) *Clostridium difficilis*: 3.4% (1/29) Cutaneous mycosis: 13.8% (4/29) Bacterial infection: 13.8% (4/29) Metabolic complications: 51.7% (15/29) Hyperglycaemia: 24.1% (7/29) Increased creatinine: 10.3% (3/29) Arterial hypertension: 10.3% (3/29) Cushing syndrome: 3.4% (1/29) Avascular necrosis of the hip: 3.4% (1/29) (length of follow-up not reported) No malignancies or life threatening complications were reported. No graft versus host disease was reported in any patient.	**Follow-up issues**: Retrospective registry review. One patient (unilateral transplant) with hand from twin brother without immunosuppressant requirement is not included in analysis. **Study design issues**: Transplantation intervention varied considerably between patients. Coverage of registry is not discussed. Reporting of outcomes is grouped by year of transplant with no overall group mean scores. Each participating centres applied their own inclusion criteria. No comparison made with baseline hand function score with prosthesis. **Study population issues**: Method of screening of patients to undergo hand transplantation is not reported. **Other issues**: None.

Abbreviations used: HLA, human leukocyte antigen.

Study details	Key efficacy findings	Key safety findings	Comments

Petruzzo (2008) cont.

antibiotics and immunosuppression.

Follow-up: 6 months to 9 years

Conflict of interest/source of funding: not reported

Total score 49.5 88

Group mean score (points) – unilateral right hand

Date	2006	2002	2001	2002	2000
Follow up	1 yr	5 yrs	5 yrs	4 yrs	6 yrs
Appearance	14	12	8.5	12.5	15
Sensibility	11	18.5	51	14	14
Movement	3.5	15	10	11.5	10
Psychological	15	15	13.5	13	15
Daily activities	7	14	9.5	12	13
Satisfaction	15	15	11	6	11
Total	65.5	89.5	68	69	78

Group mean score (points) – bilateral left hands

Date	2006	2003	2003	2000	2000
Follow up	1 yr	4 yrs	4 yrs	7 yrs	7 yrs
Appearance	12.5	12.5	14	13.5	12
Sensibility	12	10	19	17	19
Movement	13.5	15	16.5	19.5	10.5
Psychological	14	12	15	14	15
Daily activities	6	5	7	15	13
Satisfaction	6	6	11	15	15
Total	64	60.5	82.5	94	84.5

Group mean score (points) – bilateral right hands

Date	2006	2003	2003	2000	2000
Follow up	1 yr	4 yrs	4 yrs	7 yrs	7 yrs
Appearance	12.5	12.5	14	13.5	12
Sensibility	12	9	16	17	18.5
Movement	14	14.5	15	20	10.5
Psychological	14	13	15	14	15
Daily activities	7	8	7	15	15
Satisfaction	6	6	11	15	15
Total	65.5	63.5	78	95	86

Abbreviations used: HLA, human leukocyte antigen.

Study details	Key efficacy findings	Key safety findings	Comments
Kaufman C L (2009)[2] **Case report** USA Recruitment period: 1999 to 2008 Study population: Patients with previous hand amputation. **n = 5 (5 hands)** Age: 40 years mean Sex: 100% male. Patient selection criteria: Not reported Technique: Not reported **Follow-up: 2 months to 10 years**. Conflict of interest/source of funding: none	Number of patients analysed: **n = 5 hands** For all 5 patients there was a mean of 2.6 severe rejection episodes per hand. Two-point discrimination sensibility was achieved in 2 patients (too soon to determine in another patient). Functional outcome was excellent in 1 patient; 1 patient had intrinsic muscle recovery; 2 patients had good function but no intrinsic muscle recovery in 2 patients; and 1 patient had good early progress. Chronic graft rejection occurred in 1 patient at 9-month follow-up, leading to re-amputation. There were 2 cases of cytomegalovirus infection, 1 marginal zone lymphoma, 1 case of diabetes, and 1 hip osteonecrosis. **Patient 4** Patient underwent short radial amputation of right dominant hand in 2002 followed by transplantation in 2008 with immunosuppression. The patient was admitted to critical care following a 14-hour procedure for mild hypotension, and pulmonary congestion which quickly resolved. There was no severe rejection episodes to 6-month follow-up, and no major complications. Hand function allowed pick up of light objects with thumb and forefinger at 4-week follow-up. At 3-month follow-up, Carroll hand score was 67 points. Unmanageable ischaemia led to amputation of the allograft at 9 months. **Patient 5** Patient underwent amputation in 2006 followed by transplantation in 2008 with immunosuppression. An acute rejection event resolved quickly and hand function is good at very early stage follow-up of 2 months.		**Follow-up issues**: None **Study design issues**: First consecutive patients treated at the centre. Carroll score assess hand function based on grasp lifting and functional ability scores 0 to 99 (for dominant hand) higher scores better. **Study population issues**: All patients required unilateral transplantation. **Other issues**: 3 patients are probably also reported in the international registry report (Petruzzo, 2008). Full details on the 2 later cases are extracted here.

Abbreviations used: HLA, human leukocyte antigen.

Study details	Key efficacy findings	Key safety findings	Comments
Jablecki J (2010)[3] **Case report** Poland Recruitment period: 2007 Study population: Patients with previous hand amputation. **n = 1 (1 hand)** Age: 42 years Sex: 100 % male. Patient selection criteria: Not reported Technique: Donor hand matched for blood group, bone size and texture. There was a 4HLA antigen mismatch, lymphocytotoxic cross match was negative. Performed under general anaesthetic and with a tourniquet for haemostasis. Osteosynthesis aided using pins. Muscles, median and ulnar nerves sutured. Veins anastomosed where possible, and main arteries anastomosed. Immunosuppression initiated. **Follow-up:** 12 hours. Conflict of interest/source of funding: not reported	Number of patients analysed: **n = 1 hand** **Patient 1** Patient underwent amputation of left dominant arm 8 years previously at the mid forearm. Following the transplantation, no pulse oximetry signal could be detected on the thumb and index finger. Intensive bleeding was seen from fasciotomy incision made close to the operative wound. At 2 hours, a bolus dosage of heparin followed by infusion resulted in a temporary improvement of circulation to the hand and fingers. At 12-hour follow-up a vascular revision procedure was performed. Both arterial anastomoses were found to be patent; however, collaterals in the hand were thrombosed. A large clot was extracted from the radial artery on the wrist distally to the site of cannulation for arterial blood pressure measurement on the donor hand. The hand was re-amputated.		**Follow-up issues**: Single case reported from a study centre where at least 1 previous transplant had been undertaken. **Study design issues**: The donor hand was prepared according to common standards. **Study population issues**: None. **Other issues**: Graft failure might have resulted from a problem with the donor hand rather than the transplantation technique itself.

Efficacy

Quality of life

A case series of 30 patients (38 hands) reported that more than 70% of patients had improved quality of life following hand allotransplantation (absolute figures and length of follow-up not reported), and that 'most' patients returned to work[1].

Graft survival

The case series of 30 patients (38 hands) reported 100% (37/37) graft survival at 1- and 2-year follow-up; however, graft failure occurred later in 10 hands due to non-compliance with the immunosuppression regimen (timing not stated)[1]. Acute rejection episodes occurred in 85% of patients within 1-year follow-up.

A case report of 1 patient (1 hand) described re-amputation of the transplanted hand after 12 hours due to a large clot in the radial artery distal to the entry site of a cannula in the donor arm[3]. A case report of 5 patients (5 hands) described re-amputation of 1 hand at 9-month follow-up due to unmanageable ischaemia[2].

Hand function

The case series of 30 patients (38 hands) reported that 90% of patients achieved tactile sensibility, and 72% developed discriminative sensibility at follow-ups ranging from 6 months to 9 years (absolute figures not reported)[1]. For unilateral left hand transplantations performed in 1999, mean hand function score was 88 points out of 100 at 7-year follow-up. For unilateral right hand transplantations performed in 2000, this score was 78 points out of 100 at 6-year follow-up (number of hands analysed not reported).

The case report of 5 patients (5 hands) reported an 'excellent' functional outcome in 1 patient, intrinsic muscle recovery in another patient, good function but no intrinsic recovery in 2 patients, and good early progress in the remaining patient (follow-up 2 months to 10 years)[2].

Safety

Thrombosis

The case series of 30 patients (38 hands) reported that arterial thrombosis and venous thrombosis both occurred in 1 of 37 procedures (time of events not reported). Both required additional surgery[1].

Fistula

The case series of 30 patients (38 hands) reported multiple arteriovenous fistulae requiring additional surgery in 1 of 37 hands transplanted (time of event not reported)[1].

Infection

The case report of 5 patients (5 hands) describes 2 cases of cytomegalovirus infection (time of events not reported)[2].

The case series of 30 patients (38 hands) reported cytomegalovirus reactivation in 28% (8/29) of patients, herpes virus infection in 7% (2/29), cutaneous mycosis in 14% (4/29), bacterial infection in 14% (4/29), and *Clostridium difficilis* infection in 3% (1/29) of patients treated at up to 9-year follow-up[1]. Most infections were transient and reversible.

Other

The case series of 30 patients (38 hands) reported that metabolic complications occurred in 52% (15/29) of patients at up to 9 years' follow-up[1]. The same series reported that no malignancies or life threatening complications occurred. In addition, no graft versus host disease was reported in any patient.

The case report of 5 patients (5 hands) reported that 1 patient needed to be treated in critical care following the procedure because of mild hypotension and pulmonary congestion, which both resolved quickly[2]. Marginal zone lymphoma occurred in 1 patient and hip osteonecrosis in another (follow-up ranged from 2 months to 10 years).

Validity and generalisability of the studies

- Transplantation intervention technique varied considerably between and within studies.
- Long-term follow-up is important in this procedure as motor and sensory function may continue to improve over a period of years, and graft rejection may occur indefinitely.
- No details provided of validation of hand function scoring scales used to evaluate efficacy.
- Many individual case reports have been published but the majority of cases are captured in the international registry report (Petruzzo, 2008)[1].

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

There is currently no NICE guidance related to this procedure.

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Mr S Hettiaratchy (British Association of Plastic, Reconstructive and Aesthetic Surgeons), Mr N Hakim, Mr N Mamode (British Transplantation Society),

- The most important efficacy outcomes for this procedure include hand function, rejection-free survival of the transplant and patient satisfaction / subjective assessment.
- The main comparator to this procedure would be a prosthetic limb.
- The Specialist Advisers were divided in their opinion as to the current status of the procedure. One categorised it as the first in a new class of procedures; one considered it to be novel and of uncertain safety and efficacy; and one considered it to be established and no longer new.
- Adverse events that have been noted with this procedure include acute and chronic rejection (when immunosuppression stopped), poor neurological function of the hand and immunosuppression-induced diabetes.
- Additional theoretical adverse events might include malignant change / tumour and graft-versus-host disease.
- One Specialist Adviser commented that the procedure has an uncertain risk profile.
- The procedure should be limited to established composite tissue allotransplantation units.
- The procedure should be undertaken with on-site collaboration within the in-house transplantation team, with input from both transplant surgeons and

immunologists. It is being carried out by a very small number of centres by a combination of transplant, orthopaedic and plastic surgeons.

- Chronic rejection might lead to progressive loss of function.
- One Specialist Adviser commented that functional recovery is around 60%, which is similar to autotransplant.
- There has been controversy about the justification for single versus double hand transplants, and dominant versus non-dominant hands.
- The immunosuppression regimen is less toxic than that currently used for renal transplantation.
- There is an ongoing study it the USA looking to recruit 300 patients, with an estimated completion date of January 2018.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- The International Registry on Hand and Composite Tissue Transplantation (IRHCTT) is an international effort in the new area of functional restoration by performing non-life-saving allografts. It is based on the collaboration between the surgical units from around the world where hand transplantations have been performed, or other composite tissue allografts programmes have been initiated. It regularly publishes results, such as Petruzzo (2008)[1] included in table 2 of the overview.
  www.handregistry.com/index.asp?page=1
- Patients who have lost a hand are likely to be classified as disabled under the Disability Discrimination Act (DDA).
- Immunosuppression is likely to be contra-indicated in HIV-positive patients.

- The procedure is likely to be contra-indicated in patients with mental health conditions who are likely to be classified as disabled under the DDA, as motivation to use the transplanted limb is very important.

References

1 Petruzzo P, Lanzetta M, Dubernard JM et al. (2008) The international registry on hand and composite tissue transplantation. Transplantation 86: 487-492.

2 Kaufman CL, Blair B, Murphy E et al. (2009) A new option for amputees: transplantation of the hand. Journal of Rehabilitation Research & Development 46: 395-404.

3 Jablecki J, Kaczmarzyk L, Domanasiewicz A et al. (2010) Unsuccessful attempt of forearm transplantation--case report. Annals of Transplantation 15: 53-56.

Appendix A: Additional papers on hand allotransplantation

There were no additional papers identified.

Appendix B: Related NICE guidance for hand allotransplantation

There is currently no NICE guidance related to this procedure.

Appendix C: Literature search for hand allotransplantation

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	22.10.2010	October 2010
Database of Abstracts of Reviews of Effects – DARE (CRD website)	22.10.2010	n/a
HTA database (CRD website)	22.10.2010	n/a
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	22.10.2010	October 2010
MEDLINE (Ovid)	22.10.2010	1950 to October Week 2 2010
MEDLINE In-Process (Ovid)	22.10.2010	October 21, 2010
EMBASE (Ovid)	22.10.2010	1980 to 2010 Week 41
CINAHL (NLH Search 2.0/EBSCOhost)	22.10.2010	n/a
Zetoc	22.10.2010	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Hand/tr [Transplantation]
2	Forearm/tr [Transplantation]
3	Arm/tr [Transplantation]
4	(hand* adj3 (allograft* or allotransplant* or transplant* or replace*)).tw.
5	(Hand/ or Forearm/ or Arm/) and Reconstructive Surgical Procedures/
6	((hand* or forearm* or arm*) adj3 ((reconstruct* adj3 surgical*) and procedure*)).tw.
7	((hand* or forearm* or arm*) adj3 CTA).tw.
8	((hand* or forearm* or arm*) adj3 (composite* adj3 tissue* adj3 allotransplant*)).tw.
9	((hand* or forearm* or arm*) adj3 (composite* adj3 tissue*

	adj3 transfer*)).tw.
10	((hand* or forearm* or arm*) adj3 (composite* adj3 tissue* adj3 transplant*)).tw.
11	((hand* or forearm* or arm*) adj3 (composite* adj3 tissue* adj3 allograft*)).tw.
12	or/1-11
13	exp Upper Extremity/ and (Amputation Stumps/ or Amputation/ or Amputation, Traumatic/)
14	((hand* or forearm* or arm*) adj3 amput*).tw.
15	((upper and (extremit* or limb*)) adj3 amput*).tw.
16	((hand* or arm* or forearm*) adj3 los*).tw.
17	or/13-16
18	12 and 17
19	animals/ not humans/
20	18 not 19