

Anesthetic management in composite tissue transplantation (hands, face and legs)

Abstract

Background: The main problem for ideal anesthetic management of composite tissue transplantation (CTT) is the little experience and limited literature.

Methods: We report our experience in: 3 bilateral hand transplants, 1 face transplant, and 1 bilateral leg transplant performed during the period 2006-2011. 4 men and 1 woman aged 21-47 years. In the first case (bilateral hands), rapid sequence induction and anesthesia maintenance with propofol, remifentanyl and rocuronium was performed. The rest of cases were protocolized to balanced anesthesia with sevoflurane, remifentanyl and cisatracurium.

Results: The mean duration per intervention was 12.4 h SD: 1.85 h. Only the first hand transplant required dopamine. Fluid replacement and blood derivatives per intervention was 9200 SD: 2158.7 mL of crystalloids, 1750 SD: 1166.4 mL of colloids, 9.8 SD: 0.75 CH, 4.8 SD: 1.48 FFP, 1.5 SD: 0.76 of platelet pool and 0.8 SD: 0.4 g of fibrinogen. Only the first case had bleeding and coagulopathy, with a Hb of 5.1 g dL⁻¹ requiring repeat surgery. Mean extubation time was 13 h SD: 6.83 h, including the hand transplant patient that had been tracheotomized. Postoperative analgesia was controlled with NSAIDs and PCA morphine. Discharge to the ward was performed at 24h (except for 1 discharge at 48h).

Conclusion: CTT involves complex techniques, with blood loss, hypovolemia, and coagulopathy. We recommend a balanced anesthetic technique with invasive hemodynamic monitoring, placement of a high-flow central line, frequent serial laboratory tests (ABG/TEG) and maintenance of adequate graft flow.

Keywords: Composite tissue allograft; Bilateral hand transplant; Vascular microsurgery and anesthetic management

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Introduction

Compound tissue transplantation is a new therapeutic option in reconstructive surgery for an ever-growing group of patients. The main feature is the presence of tissues from different cell types: skin, tendons, nerves, blood vessels, muscles, and high immunogenic content bone, requiring an immunosuppressive regimen capable of preventing rejection of each tissue.¹⁻³ CTT is not undertaken to save or extend patient life but to improve their quality of life. It is a complex procedure, feasible thanks to the progress in microsurgery techniques, the development of solid organ transplants, experience in anesthetic management and new immunosuppressive drugs, requiring an optimum coordination of a multidisciplinary team (surgeons, anesthesiologists, immunologists, rehabilitators and pharmacologists), to minimize ischemia times, optimize surgical conditions and achieve the best results.³⁻⁶

In September 1998 a new milestone in the history of medicine took place in Lyon, the first transplant of hand.⁵ Thirty-four years would have to pass and tremendous development of immunosuppressive therapy before achieving the favorable clinical course that microsurgery techniques have made possible in Ecuador in 1964 and which had failed due to organ rejection only 2 weeks later.⁶ Since then these transplants were performed episodically in different countries,³ including, also in Lyon, the first bilateral hand transplant in January 2000, with the creation in 2002 of a world registry to promote cooperation between teams developing hand transplantation.^{4,7,8}

In June 2008 the International Registry on Hand and Composite Tissue Transplantation.⁹ had recorded 32 procedures, confirming that hand transplantation is a feasible procedure, while publication of

the results of the pioneering groups and of long-term patient follow-up revealed the good outcome of the procedure from all standpoints.¹⁰⁻¹²

Selection of donor/recipient of limb transplants

Lifelong triple immunosuppressive therapy is the greatest disadvantage.¹³ Our criteria only include bilateral transplantation because of the tremendous functional gain as compared to the risks of immunosuppression, though these criteria could change with the development of new immunosuppressive therapies with fewer side effects.¹⁻³

Inclusion criteria for the recipient

Age 18-55 years, able to understand and accept the complexity of the surgical procedure and assume the risks of immunosuppression, have preserved or reconstructed vascularization and muscles, adequate family and social support for psychological stability and prolonged rehabilitation. Negative lymphocytotoxic antibodies (anti-HLA).¹⁻³

Inclusion criteria for the donor

Share blood group, sex, and race with recipient. Similar weight, height and skin texture. Have no tattoos or marks in body part to be transplanted. Donors with prior limb operations should preferably be avoided. HLA compatibility between donor and recipient is not essential. Negative serologic testing for HIV, HBV, HCV, syphilis, and toxoplasmosis. For CMV and EBV, positive donor and negative recipient crossmatching is avoided, but is not an exclusion criterion.^{1,3}

Relative contraindications of the recipient

Brachial plexus lesion, diabetes mellitus, blindness, neoplastic disease in the past 10 years, recurrence of an infectious process.^{1,3}

Selection of donor/recipient of face transplant

Patients with severe deformity with functional repercussions who have exhausted or do not have available the options of reconstruction with autologous tissue.^{3,14} Immunosuppressive therapy and risk of death in the case of loss allograft loss are the greatest disadvantages.^{12,13,15} The criteria are similar to limb transplantation, except the age limit rises to 65 years, since nerve regeneration in recovery of muscle function is not the priority.³

Anesthetic considerations

Tissues to be transplanted undergo primary ischemia, whose severity and seriousness is proportional to time, which is tolerated differently by different tissues and which we cannot influence.^{16,17} We will use as a basis the anesthetic management of reconstructive microsurgery that is most similar combining it with the anesthetic techniques of other solid organ transplants.^{16,18,19}

The anesthetic management of the transplant needs to pay attention to the physiological variables regulating microcirculation, i.e., vascular tone, circulatory pressure, blood volume and viscosity, because adequate blood supply to tissues grafted by anastomosed vessels will be crucial to their survival, anesthesia, with its influence on regional and systemic circulation, being a clearly determining factor.^{20,21}

The graft, as it is a denervated tissue, does not have an adequate response to sympathetic stimulation, so surgical handling, cold or reflex activity may cause vascular spasm. In accordance with the Laplace and Poiseuille laws explaining blood flow, any cause of vasoconstriction must be avoided to ensure proper flow, maintaining a maximum dilatation.^{20,22} The intraluminal factors refer to the need for maintaining an adequate perfusion pressure and intravascular volume to ensure flow to the transplanted tissue. A low blood viscosity also needs to be obtained, with hematocrits around 30%.²³ by means of normovolemic dilution, as well as preventing platelet adhesion and aggregation to vascular wall to avoid thrombosis phenomena in the transplanted vessels.^{1,2,16,17} The preoperative evaluation according to the standards established by the Spanish Society of Anesthesiology and Resuscitation (SEDAR).²⁴ A peculiarity of face transplant is the high presence of VAD, so we must have adequate material and training, even to assess the possibility of performing tracheotomy before induction under local anesthesia and sedation.^{25,26} The assessment should include a limb angiogram to know the status of the recipient vessels,³ in addition to radiographic, electromyographic and neurophysiological assessment of these vessels. Without forgetting the previously mentioned psychological evaluation.³ Perform the correct postural measures to prevent lesions due to pressure and peripheral neuropathy together with systems of intermittent compression of lower limbs for prevention of venous stasis and thrombosis.²³

Intraoperative monitoring will include ECG, noninvasive blood pressure, peripheral pulse oximetry, EtCO₂, urine output, temperature, BIS and TOF. A high-flow central line will be placed, recommending insertion of a Swan-Ganz catheter and having available rapid infusion and blood recovery systems.^{1,2,14} Blood pressure will also be monitored invasively for correct hemodynamic management, and some degree of controlled hypotension may be useful during the initial phase to decrease bleeding, subsequently maintaining a slightly hyperdynamic state to optimize oxygen transport to tissue, and frequent were blood samples will be drawn to perform serial laboratory tests, arterial blood gas tests and thromboelastograms, to help to determine blood losses and correct electrolyte, acid-base balance and coagulation abnormalities.^{27,28}

Immunosuppressant protocol includes intraoperatively: corticosteroids: 500 mg of methylprednisolone, together with a lymphocyte depleter: alemtuzumab 30 mg vs basiliximab 50 mg, which are humanized monoclonal antibodies against the CD52 antigen, causing a profound depletion of T-lymphocytes with release of tumor necrosis factor (TNF), interleukin-6 and interferon. These have a high incidence of adverse reactions: skin rash, hypotension, and even anaphylactic shock, so premedication with dexchlorpheniramine 50 mg and acetaminophen 1 g is recommended. In the postoperative period, immunosuppressive treatment is maintained with corticosteroids, a calcineurin inhibitor (tacrolimus vs cyclosporine), and mycophenolate mofetil.^{3,29,13}

Anesthetic technique

No controlled study has shown that one anesthetic technique is superior to another. Although the literature recommends balanced general anesthesia, the combined use of continuous local anesthetic techniques (epidural catheter, intradural or brachial plexus) has the advantage of improving the perfusion of transplanted tissues by vasodilation and increasing the flow caused by sympathectomy, preventing vasospasm and reducing the incidence of thrombotic events. Although it has disadvantages such as hypotension due to sympathectomy, the “steal phenomenon” by vasodilatation of recipient tissue versus denervated implanted tissue and the possibility of increasing intraoperative bleeding.^{30,31} Thus, in view of the lack of experience and evidence, it was decided not to include locoregional procedures in the protocol.^{1,3} Although there are other groups (such as Pittsburgh) that include local procedures for arm transplantation by placing echo catheters directed to the supraclavicular level. Administration of an initial bolus with a short-acting local anesthetic, confirmation of block function and provision of initial analgesia for the tourniquet. No starting the local anesthetic infusion until the postoperative period provided the patient is hemodynamically stable.²

Induction

There is no ideal hypnotic or technique, and the most appropriate according to the patient's condition should be used. Perform a rapid sequence induction in any patient considered a full stomach.¹⁴

Maintenance

The use of halogenated appears to be more prevalent than intravenous anesthesia with propofol. It has been shown that the sevoflurane has beneficial effects on microcirculation compared to propofol by decreasing plasma extravasation into the interstitial space, preventing the occurrence of edema. In addition, the peripheral vasodilator effect predominates over myocardial depression and there is scientific evidence of the protective factor of halogenated agents injury due to ischemia-reperfusion. For analgesia, we use opiates, remifentanyl being the one that offers greater hemodynamic stability and given its short half-life allows us to adapt rapidly to significant hemodynamic changes. A continuous neuromuscular block is maintained.^{17,21}

Management of volemia

Bleeding surfaces are extensive and bleeding is continuous despite the use of ischemia systems through tourniquets on limb transplants, worsening at the times of reperfusion. Fluid replacement and blood components should be based on invasive monitoring, urine output and serial laboratory tests (ABG/TEG). In the choice of fluid therapy, crystalloids have the theoretical disadvantage of migrating quickly from the vascular bed to the interstice, so they are less effective

than colloids to maintain volume expansion and cause tissue edema. Colloids are recommended due to their osmotic effect, increasing plasma volume, reducing plasma viscosity, and enhancing rheology and improving blood flow without leading to major changes in haemostasis.^{27,28}

Normovolemic hemodilution techniques will be useful to us to reduce blood viscosity, and a hematocrit around 30% should be maintained in order to ensure good tissue oxygenation. We will use vasoactive drugs in the presence of hypotension refractory to fluid therapy and blood derivatives. It is recommended to avoid alpha-agonist drugs, and the drug of choice is low-dose dobutamine as it increases flow in donor and recipient vessels. Dopamine at beta dose can also be used to increase flow at the expense of improving cardiac contractility.²²

Postoperative control in resuscitation

The first hours are crucial to prevent the occurrence of ischemia secondary to the graft, so we should avoid peripheral vasoconstriction

Table 1 Status at start of procedure: after premedication with paracetamol and dexchlorpheniramine and antibiotic prophylaxis with amoxicillin/clavulanate. TIVA: propofol, remifentanyl, and rocuronium. *mannitol infusion as prophylaxis for acute tubular necrosis. Balanced anesthesia: sevoflurane, remifentanyl, and cisatracurium

Patient	Anesthetic induction	Anesthetic maintenance	Site of catheter placement	Immunosuppressive therapy
1	Rapid sequence	TIVA	Right femoral artery and vein	Alemtuzumab and methylprednisolone
2	Rapid sequence	Balanced anesthesia	Right femoral artery and right internal jugular vein. (high flow)	Alemtuzumab and methylprednisolone
3	Rapid sequence	Balanced anesthesia	Right femoral artery and right internal jugular vein. (high flow)	Alemtuzumab and methylprednisolone
4	Tracheotomy under local anesthesia.	Balanced anesthesia	Right foot artery and vein right basilic vein (cavafix) and femoral vein (high flow)	basiliximab and methylprednisolone
5*	Rapid sequence	Balanced anesthesia	Right radial artery and right internal jugular vein (high flow and Swan-Ganz)	basiliximab and methylprednisolone

Table 2 Follow-up parameters of the intervention and postoperative analgesia with NSAIDs and PAC morphine

Patient	Duration IQ (h)	CH	FFP	Platelets (pool)	Fibrinogen (g)	Crystalloids (ml)	Colloids ml	Urine Output ml	Ischemia Time (h)	PD	MV Disconnection (h)
1	10	10	3	1	1	7,500	0	2,700	09-Aug	D.beta	10
2	11	10	4	1	1	8,500	1,500	2,800	8.5/9	X	11
3	12	9	6	0	0	7,000	1,000	3,100	9/9.5	X	24
4	15	11	6	2	1	13,000	1,000	7,750	5.45	X	6
5	14	9	7	2	1	10,000	3,500	5,200	4/5.5	X	5
Mean	12.4	9.8	4.8	1.5	0.8	9,200	1,750	4,310	7.55	-	11.2

Table 3 Total hospital and recovery room stay. Recovery: Postsurgical critical care unit

Patient	Hospital stay	Recovery room stay
1	22 days	24 h
2	13 days	24 h
3	15 days	48 h
4	25 days	24 h
5	21 days	24 h
Mean	19.2 days	28.8 h

Discussion

Composite tissue transplantation is an important technically feasible procedure thanks to the advances in microsurgery techniques, the development of solid organ transplant and the great experience in anesthetic and associated postoperative management, together with new immunosuppressive drugs capable of preventing rejection of tissues with high immunogenic content, achieving satisfactory

using adequate analgesia and sedation, adequate oxygenation, maintaining normothermia, avoiding vasoactive drugs, with a slightly hyperdynamic status with a high cardiac output and low peripheral vascular resistance. The implanted tissue will be monitored by pulse oximetry, color, temperature, and vascular filling, to detect arterial vasospasm, possible arterial or venous thrombosis and bruising. Early platelet aggregation will be initiated, performing serial laboratory tests and if possible a fast track.^{21,32,33}

Materials and methods

A retrospective observational study. We report our experience in CTT: 3 bilateral transplants hands, 1 transplant face and 1 bilateral transplant lower limb that chronological order, performed during the period from 2006 to 2011, as anesthetists integrated into a multidisciplinary team needing an optimum coordination to minimize ischemia times and optimize the surgical conditions to achieve the best results. The review was made via PubMed including up to September 2012. Data were collected by reviewing patients' medical records between January and February 2013 (Tables 1-3).

clinical and functional results, requiring an adequate adherence to immunosuppressive therapy and intense rehabilitation.³⁴⁻³⁷

In our first patient, surgery was performed by a single anesthetist using the TIVA technique, where the lack of experience, difficulty in quantitating bleeding, and insufficient laboratory measurements caused us to fall behind transfusion needs in the final part of the procedure with the result that the patient became unstable and required support with dopamine and multiple postoperative transfusions with surgical review within a few hours due to venous hematoma in the right hand. A protocol was subsequently established in which it was recommended that surgery be performed by two anesthetists using balanced general anesthesia because of the benefits of sevoflurane on microcirculation and the protective factor in injury due to ischemia-reperfusion. Analgesia was performed with remifentanyl because its pharmacokinetic and pharmacodynamic characteristics allow for greater hemodynamic stability and a short half-life allows us to adapt rapidly to significant hemodynamic changes.^{1,14,17,21}

The combined use of continuous locoregional procedures has the advantages of improving perfusion, preventing vasospasm and decreasing thrombosis, but with the disadvantages of hypotension, bleeding and the “steal phenomenon”, so it was decided not to be included in the initial protocol and provide postoperative analgesia using multimodal analgesia with PCA morphine and NSAIDs, obtaining excellent results with low VAS scores.^{1,2,30,31} Although currently based on the results obtained by other groups, we can recommend its use in the postoperative period for postoperative analgesia and to enhance the flow of transplanted tissues. Placement of a high-flow central line is recommended, to have a rapid blood infusor and recuperator, invasive monitoring with arterial and pulmonary catheter, together with frequent serial laboratory tests, to optimize hemodynamic management, to determine blood losses and coagulopathies and to be able to correct significant electrolyte and acid-base balance abnormalities due to the long periods of ischemia and reperfusion that may even cause arrhythmias including asystole.^{27,28} Use of vasoactive drugs will depend on hemodynamic status and visual inspection by the surgeon of the efficacy of microvascular anastomoses, using dobutamine and/or dopamine in inotropic doses and avoiding alpha-agonist drugs due to their vasoconstricting effect.²² With adequate urinary flow to maintain a urine output of 1 ml/kg/h and prevent renal dysfunction.³⁸

The immunosuppressant protocol includes a lymphocyte depleting agent, corticosteroids, a calcineurin inhibitor and mycophenolate mofetil, achieving for the first time a 100% success rate in allograft preservation during the first year after transplantation. We should consider the effects and interactions of immunosuppressive induction, particularly that caused by lymphocyte depleters, because of their high incidence of adverse reactions and we should therefore premedicate all patients.^{13,29} The most common adverse effects of immunosuppression are hyperglycemia, hypertension, and dyslipidemia. In all our patients, tacrolimus was replaced by sirolimus because of the increase in serum creatinine which improves after switching.²⁹ Postoperative management in the critical care unit should be aimed at preventing peripheral vasoconstriction using an adequate analgesia and sedation, maintaining normothermia, oxygenation and adequate volemia, together with monitoring of the implanted tissue, serial laboratory tests, starting platelet aggregation and promoting early discharge from critical care units.^{1,2,3,14}

Recommendations

CTT involves long and complicated techniques, with a significant blood loss, with great insult caused by ischemia and reperfusion which usually results in hypovolemia and coagulopathy. We recommend a balanced anesthetic technique, which may be combined with continuous locoregional anesthetic techniques for postoperative analgesia, together with invasive hemodynamic monitoring, placement of a high-flow central line and having available a rapid fluid infusor and blood recuperator. Perform frequent serial laboratory tests (ABG/TEG), maintain an adequate flow to the graft to prevent hypotension, vasospasm and use of vasoactive drugs and try to improve oxygen transport to optimize CTT function.

We may conclude that although a greater experience is needed, from the introduction of the anesthetic protocol no patient required support with catecholamines or experienced complications requiring repeat surgery.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the European Journal of Anaesthesiology.

Conflicts of interest

There is no conflict of interest.

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