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GENERAL INFORMATION

Current status of intestinal transplant in adults

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Abstract
Intestinal transplant is a surgical procedure internationally proposed as an alternative treatment for patients with irreversible intestinal failure due to short bowel syndrome, intestinal ischemia, Crohn's disease, volvulus, trauma, necrotising enterocolitis, patients who are destined to permanent therapy by total parenteral nutrition and those who present with severe complications of these disorders. There are several surgical techniques for intestinal transplant such as isolated intestinal transplant, hepatointestinal and multivisceral transplant. Among the main complications are technical-surgical and non-surgical (ischemia reperfusion injury, acute rejection, chronic rejection, post- transplant lymphoproliferative disease, infections and graft versus host disease). Immune therapy plays a primary role in the survival of both patient and graft. The graft can be monitored immunologically by expression of specific markers (CD154, calprotectin and nucleotide polymorphisms) or macroscopically and microscopically by endoscopy and biopsy, mainly of ileum and jejunum. Intestinal transplant as a whole is a broad field of medical research worldwide which, although has improved the lives of many patients, still cannot be considered a definitive treatment of first choice for patients with irreversible intestinal failure.

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PALABRAS CLAVE
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Intestino;
Intestino aislado;
Hepatointestinal;
Multivisceral;
Nutrición parenteral total;
Inmunosupresión

Estado actual del trasplante de intestino en adultos

Resumen
El trasplante intestinal es un procedimiento quirúrgico propuesto internacionalmente como una alternativa de tratamiento para pacientes con insuficiencia intestinal irreversible secundaria, entre otros, a síndrome de intestino corto, isquemia intestinal, enfermedad de Crohn, vólvulo, trauma, enterocolitis necrosante, pacientes que están destinados a terapia con nutrición parenteral total de por vida y que cursan con alguna complicación grave de esta. Existen varias técnicas quirúrgicas de trasplante intestinal, como el intestinal aislado, el hepatointestinal y el multivisceral. Dentro de las principales complicaciones se encuentran las técnico-quirúrgicas y las no quirúrgicas (lesión por isquemia reperfusión, rechazo agudo, rechazo crónico, enfermedad linfoproliferativa postrasplante, infecciones, enfermedad de injerto contra huésped). La terapia inmunológica juega un papel primordial en la sobrevida del paciente y del injerto. El injerto puede vigilarse inmunológicamente por expresión de marcadores específicos (CD154, calprotectina y polimorfismos de nucleótidos), o puede vigilarse macro y microscópicamente por medio de endoscopia y toma de biopsia de íleon y yeyuno. El trasplante intestinal, en su conjunto, es un campo amplio de investigación médica a nivel mundial que, si bien ha mejorado la vida de muchos pacientes, todavía no se puede considerar como tratamiento definitivo y de primera elección en pacientes con insuficiencia intestinal irreversible.

Background

Short bowel syndrome is a result of the loss of the physical and functional segments of the small intestine, which causes a clinical profile of metabolic abnormalities due to reduced functional absorptive surface and is manifested by the inability to retain all dietary micro- and macronutrients such as proteins, electrolytes, carbohydrates, etc.[1,2].

A *short bowel* is defined when a non-functional segment does not allow an adequate absorption, resulting in the need for nutrient, water and electrolyte supplements to maintain the body's metabolism and requirements[1,2].

Intestinal failure is defined as a significant reduction in functional bowel mass below the threshold necessary to maintain a balance in growth, hydration and electrolyte concentrations in the patient; short bowel syndrome causes the most common intestinal failure, especially in paediatric patients[3].

Intestinal failure is defined when parenteral nutrition is needed to maintain the patient's nutritional balance and metabolism for at least 3 months[4]. The cause is massive intestinal loss either from surgery, ischemia-necrosis or birth defects, etc.

Treatment of short bowel syndrome focuses on maintaining the patient's electrolyte and nutritional balances, which in the case of the most serious forms involves administration of parenteral nutrition. However, in recent years, therapeutic advances in short bowel syndrome are able to offer some patients the ability to not rely on parenteral nutrition or intravenous fluids. The identification of patients who could benefit from new therapeutic strategies such as growth hormone, octreotide, analogues of *glucagon-like peptide-2* [GLP-2] or even intestinal transplant, which depend on a correct diagnosis and classification, is complicated by the different definitions of short bowel and intestinal failure syndromes in the medical literature.

"Intestinal failure" is the result of obstruction, dysmotility, surgical resection, congenital defect or absorption loss associated with the disease, which is characterised by the inability to maintain energy-protein and electrolyte or micronutrient balances (Table 1). The severity of clinical fea-

Table 1 Causes of short bowel syndrome and intestinal failure in adults and children

Adults	Children
Vascular accidents	Chronic intestinal pseudo-obstruction
Superior mesenteric artery embolism	Intestinal tumour resection
Superior mesenteric artery thrombosis	Volvulus
Superior mesenteric vein thrombosis	Multiple resections for Crohn's disease

tures depends on several factors including size and site of the resection, presence or absence of the ileocecal valve, functioning of the remaining digestive organs and adaptability of the intestinal remnant (Fig. 1).

The long-term outcome is primarily determined by the patient's age and the disease complications. The pathophysiological changes that occur in short bowel syndrome relate mainly to the loss of intestinal absorption surface, the rapid intestinal transit, gastric hypersecretion, inactivation of pancreatic enzymes and loss of bile salts. Malabsorption of nutrients results in malnutrition and weight loss, diarrhoea, steatorrhea, vitamin deficiency and electrolyte imbalance depending on the anatomical sector lost[5-8].

Intestinal adaptation is used in the clinical setting to indicate intestinal function recovery after an intestinal resection and begins 48 h after surgery; this process seeks to restore the intestinal absorption of micro- and macronutrients prior to bowel resection and determines whether the intestinal failure will be permanent or temporary. The maximum intestinal adaptation in adults is estimated to be 2 years, but in children it can last >3years.

Medical rehabilitation

The overall objective of medical rehabilitation is that the patient leads the most normal life possible, with less dependence on parenteral nutrition. Optimal management should improve patient survival. Intestinal rehabilitation is the process of improving intestinal absorption and function through a modified diet, enteral nutrition, oral rehydration, antidiarrhoeal, antibiotics and antisecretory solutions and use of growth factors, all to maintain a favourable nutritional status.

The most important therapeutic goal of short bowel syndrome is to maintain the nutritional status of the patient, especially through support by parenteral nutrition in the immediate postoperative period. This therapy involves the administration of energy and protein substrates, fluids, electrolytes, minerals, vitamins and micronutrients to the patient. Most patients require 25-30 kcal/kg per day and 1.0-1.5 g of protein per kg per day[9].

Loss of fluids and electrolytes in the gastrointestinal tract in the immediate postoperative period may be significant, so being aware of the patient's requirements for fluid and preventing dehydration is vitally important[9].

Enteral nutritional support should be started as soon as possible after surgery when the ileus has been resolved. This step is vital to maximising intestinal adaptation and preventing complications related to parenteral nutrition. The intestinal remnant length has important prognostic implications for nutritional support. Patients with >180 cm of small intestine residual do not generally require parenteral nutrition, those with >90 cm of small intestine and, in particular, with colon cancer generally require parenteral nutrition for at least 1 year, and those who have <60 cm of small intestine are likely to require permanent parenteral nutrition.

There are multiple studies assessing its administration together or independent from GLP-1 and -2 secreted in the distal intestine as these favour intestinal absorption and its growth, showing improvement in clinical symptoms such as decreased diarrhoea and an increase in absorption, which are considered the main hormonal stimulus for intestinal adaptation. In the absence of a colon, GLP-2 has been shown to induce hyperplasia of villi on day 4 of administration in animals and in patients[10,11]. In humans, treatment with GLP-2 enhances intestinal absorption modestly (3.5%, mainly due to better protein absorption) and the nutritional status in patients with short bowel syndrome with resection of terminal ileum and colon whose postprandial secretion of GLP-2 is affected[10,11].

Surgical treatment for short bowel syndrome

The surgical approach to patients with short bowel syndrome depends on several factors; the *type of nutritional support* is the main reason for surgery because at least half the patients who have short bowel syndrome can only be sustained with enteral nutrition.

Surgery should be considered with great caution and only if patients show signs of worsening malabsorption or if they are at risk of requiring parenteral nutrition or have other symptoms related to malabsorption. Nearly half the patients who remain stable during the long-term when treated with parenteral nutrition are candidates for surgery, and this will be done with the aim of weaning the patient off this treatment. In a study by Javid et al.[7] it was observed

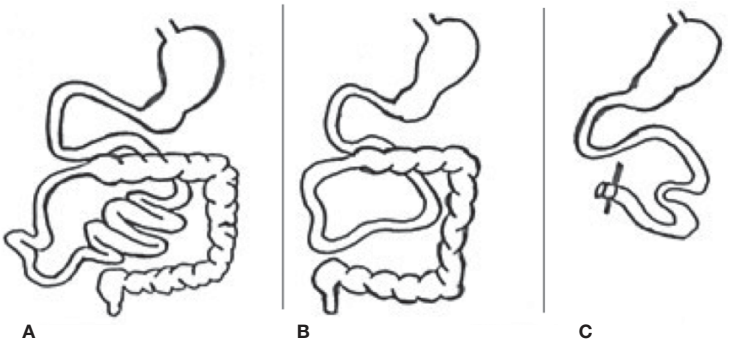

Figure 1 The three most common types of intestinal resection and anastomosis observed in patients with short bowel syndrome. A) Ileocolonic anastomosis. B) Jejunum colonic anastomosis. C) Terminal jejunostomy.

that the transverse serial enteroplasty improved enteral tolerance by 80%, and 60% of patients achieved enteral autonomy, such that they also improved the need for caloric intake in parenteral nutrition.

Patients who develop significant and persistent complications or those with recurrent complications found in parenteral nutrition have more compelling reasons for surgery and are patients who should be considered for intestinal transplant because many may die before their time.

Parenteral nutrition in sick patients with permanent intestinal failure has many complications. Therefore, in certain cases, intestinal transplant is the only therapeutic alternative; the aim is the replacement of the absorptive device that is non-existent or has been lost or damaged by the disease. However, there are different types of surgical options for patients with short bowel syndrome; the decision of which procedure depends on the patient's intestinal anatomy and clinical condition (Table 2).

Biomarkers

Citrulline is an amino acid that is produced exclusively by enterocytes. Its value was studied as a biomarker of functioning enterocyte mass in patients with intestinal failure due to short bowel syndrome and its relation to digestive tolerance. Despite advances in intestinal transplant over the past decades, acute rejection remains the most common complication and the most common cause of graft loss. Its diagnosis is usually too late because the diagnostic tools currently available are the combination of clinical evolution with endoscopy and a histology of biopsies, an invasive method withpotentially serious complications. Determining the plasma citrulline as a screening test for early detection of graft dysfunction has been suggested because in this situation a significant decrease in value occurs. A value of citrulline >19 mmol/l is associated with good enteral tolerance and is a predictor value for parenteral weaning. Fitzgibbons et al.[12] demonstrated that citrulline values of <12 mmol/l could not be detected as they showed severe metabolic complications.

Intestinal transplant

Since the beginning of last century there has been research into surgical, clinical and immunological experiences of intestinal transplant led by a transplant surgeon at the University of Minnesota. Lillehei was the first surgeon in the world to carry out this procedure, initially experimenting on animals (dogs) and then performing the procedure on humans[13-15].

The success of these first attempts was limited by surgical inexperience and a lack of physiological knowledge, but mainly by insufficient immunological knowledge. Over time, these limitations have been reduced. Currently, intestinal transplant has become a palpable surgical reality thanks to the birth of immune therapy that has created specialised referral centres in this field, the formation of multidisciplinary teams, the establishment of a grant infrastructure that has protocols for the inclusion of donors and recipients, etc.

Early intestinal transplant

The father of intestinal transplants is without a doubt Richard Carlton Lillehei[13] who, with the methodological thoroughness of his experimental work and the precision of his clinical observations, built models that have not been matched[13-15]. He made enormous advances in the field of shock, organ preservation and transplant, being the first surgeon to perform pancreatic and intestinal transplants worldwide. His first transplant was performed in March 1967 on a 46-year-old woman who had undergone extensive resection of the small intestine after having undergone an extensive mesenteric thrombosis. The patient died hours after surgery and an autopsy revealed extensive thrombosis of the portal vein and vena cava thrombosis[16]. Years later, ac-

Table 2 Surgical treatment for short bowel syndrome

Clinical status	Intestinal anatomy	Surgical therapy
Only enteral nutrition	Adequate length with normal diameter (>120 cm)	Optimise intestinal function, recruit additional length
Bacterial overgrowth	Adequate length with dilated bowel	Treat the intestinal obstruction
Accelerated intestinal transit, need for parenteral nutrition	Marginal length with normal diameter (60-120 cm)	Recruit additional length methods for decreasing intestinal transit
Bacterial overgrowth, need for parenteral nutrition	Marginal length with dilated bowel	Lengthen the intestine
Need for parenteral nutrition	Short length with normal diameter (<60 cm)	Optimise bowel function
Bacterial overgrowth, need for parenteral nutrition	Short length with dilated bowel	Lengthen the intestine
Complications for parenteral nutrition	Short length	Intestinal transplant

cording to Gondolesi et al.,[17] Starzl and his team conceived the first multivisceral transplant and, as part of the graft, not only included the intestine but also the liver, stomach, pancreas, duodenum and colon.

A long path has been trodden since the first successful transplant occurred, which in the literature does not appear until the 1990s, published by Grant et al. in Canada. The first combined transplant of liver and small intestine was carried out successfully by the Goulet group in Paris. In the first transplants, cyclosporine was used as the main immunosuppressant medication. The reason that this type of transplant was possible was because of the development of other effective immunosuppressants such as the discovery of FK-506 tacrolimus[17].

Indications for intestinal transplant

All patients with irreversible intestinal failure are potential candidates for intestinal transplant. This syndrome is defined as a situation in which the intestine loses its ability to maintain protein energy, fluids, electrolytes or a balance of micronutrients, despite a maximum administration by a normal diet, which is insufficient to maintain the body's metabolism[18]. In most patients, intestinal failure is secondary to the presence of short bowel which, according to the data published in the report by the international registration of intestinal transplant in Washington in September 2011, state the main causes of intestinal transplant are, in order of frequency: 65% due tosecondary short bowel syndrome (ischemia, Crohn's disease, volvulus, trauma and necrotising enterocolitis), 15% motility disorders, 10% retransplant, 8% tumours and 2% mucosal defects that cannot be maintained on total parenteral nutrition because of its serious complications.

There are recommendations by the American Gastroenterological Association that define "total parenteral nutrition failure" as the development of one or more of the following complications[19]:

- *Liver failure secondary to total parenteral nutrition.* Serum bilirubin and/or elevated liver enzymes, hepatosplenomegaly, thrombocytopenia, portal hypertension, coagulopathy, liver fibrosis or cirrhosis[19]. The incidence of liver damage because of total parenteral nutrition is greater in the case of short bowel syndrome among the adult population than the child population and is currently the leading cause of death. In children, cholestasis fibrogenesis and biliary cirrhosis are typical complications. In adults, however, the typical early finding is steatosis.
- *Loss of at least two of the major central venous vessels.* Subclavian, jugular or femoral veins. This may result from thrombosis or repeat sepsis in adults.
- *Frequent recurrent sepsis.* Related to central pathways: two episodes of systemic sepsis related to catheter infection per year, an episode of fungemia related to the pathway, septic *shock* or adult respiratory distress syndrome.
- *4Nutritional requirements for life.* Understood as such from the second year of initiation of total parenteral nutrition.
- *Poor quality of life secondary to intestinal failure.* Frequent hospitalisations due to septic, metabolic or surgical complications, severe dehydration, etc. resulting in a poor quality of life; these patients should be considered for intestinal transplant even in the absence of complications from total parenteral nutrition.
- *Thrombosis of the mesenteric-portal axis.* The most common cause of venous thrombosis are hypercoagulable states and trauma. Patients with thrombosis of mesenteric-portal axis due to deficit of proteins S and C should be referred to an intestinal transplant centre to assess hepatointestinal transplant.

Contraindications

- *Absolute.* A history of uncured cancer, HIV infection, heart or severe lung failure, uncontrolled sepsis, neurodegenerative diseases and systemic autoimmune diseases and severe immune deficiency.
- *Relative.* Age >60 years, low nutritional status and a number of previous laparotomies.

Main intestinal transplant surgical techniques and indications

Isolated intestinal transplant

Indications

Patients with chronic irreversible intestinal failure not associated with the terminal failure of other intra-abdominal organs and with a need for continuous total parenteral nutrition in the long-term and a high incidence of recurrent complications induced by total parenteral nutrition are candidates[20]. It is the most common type of transplant in adults at 55% according to the Intestinal Transplant Registry (ITR) [21].

Included organss

The entire small intestine, with or without the colon, or part of it[22,23].

Surgical technique

The intestine is extracted from the angle of Treitz to the terminal ileum, with the superior mesenteric artery and the superior mesenteric vein to the portal vein. Graft arterialisation can be done from the superior mesenteric artery of the receptor or the infra-renal aorta, if the former is retracted or of small calibre as in most cases with short bowel syndrome. In this case it is usual to use the donor's arterial interposition grafts. Venous drainage is towards the superior mesenteric vein or the inferior vena cava, an alternative for cases where the former is not accessible or where there is liver fibrosis that might compromise the venous return of the graft. Should the thrombosed inferior vena cava be below the renal veins, the left renal vein or inferior mesenteric vein can alternatively be used[22,23].

Finally, distal reconstruction is performed by an end ileocolic anastomosis, at ~20 cm from the end of the ileum, which is externalised by an end ileostomy necessary for monitoring the graft with ileoscopies and protocol biopsies.

Hepatointestinal transplant

Indications
Indications are the coexistence of intestinal and liver failure, usually secondary to irreversible liver disease induced by total parenteral nutrition in the long-term such as severe cholestasis, portal hypertension and irreversible significant hepatocellular lesion and portomesenteric venous thrombosis.

Included organs
Also called "en bloc" because in addition to the liver and intestine, the graft includes the pancreatoduodenal complex.

Surgical technique
The implant will be initiated by anastomosis between the graft's suprahepatic vena cava and the stump of the receptor's three suprahepatic veins. Following that, the anastomosis is conducted between the aorta of the hepatointestinal block and the receptor's supraceliac or infrarenal aorta (which has been dissected after extraction of the native liver). At this time, the graft is reperfused and purged with blood through the infrahepatic vena cava of the graft, after which it is sutured with mechanical stapler apparatus. Following the reperfusion, a cholecystectomy is performed. Side-to-side anastomosis is used in the reconstruction of the intestinal transit (preferably termino-terminal) between the duodenum or proximal jejunum of the graft to the receptor's duodenum or jejunum and side-to-end anastomosis between the graft terminal ileum of the graft and receptor's colon. Finally, distal reconstruction is performed by an end ileocolic anastomosis, at ~20 cm from the end of the ileum, which is externalised by an end ileostomy necessary for monitoring the graft and protocol biopsies.

Multivisceral transplant

Indications
This type of transplant is indicated in cases of extensive intraabdominal disease, including locally aggressive tumours but without evidence of metastatic disease (such as desmoid tumours), wide portomesenteric thrombosis/splenic vein thrombosis, extensive arterial ischemia or alteration of intestinal and gastric motility syndromes[24].

Included organs
Included organs are stomach-duodenum-pancreas-jejunum-ileum and liver block.

Surgical technique
The difference with the combined transplant is that during abdominal exenteration the stomach, duodenum-pancreas and spleen are also removed, so the portal-caval *shunt* should not be removed to ensure venous drainage. The implant is made en bloc performing a suprahepatic vena cava anastomosis, implanting an arterial duct on the donor's aorta to the recipient's infrarenal aorta. Intestinal continuity is restored proximally by performing a gastroesophageal anastomosis, carrying out a pyloromyotomy and pyloroplasty in addition to placing the gastrojejunostomy tube at proximal and distal levels. As in the above procedures an ileocolonic anastomosis with chimney ileostomy is performed. The current trend is to leave the spleen as part of this procedure and the need to include a kidney graft is not uncommon, which is left in continuity with the inferior vena cava.

Major complications of the intestinal transplant

Intestinal transplant complications can be classified as:

- *Surgical*. Arterial or venous thrombosis, suture failure and intestinal bleeding.
- *Non surgical*. Ischemia-reperfusion injury, acute cellular rejection, infections, graft-versus-host disease, proliferative disease and nutritional problems.

Ischemia-reperfusion injury

The interruption of blood flow to an organ, with its subsequent lack of oxygen and nutrients, is an intrinsic phenomenon during various surgical procedures such as intestinal transplant. Once the blood flow and oxygen supply is restored, reperfusion increases the damage caused by the ischemia period, aggravating the damage at a cellular level. This phenomenon is known as ischemia-reperfusion injury[25].

The harmful effects of modifying the ATP catabolism increases due to the production of various substances including reactive oxygen species, cytokines, adhesion molecules and vasoactive agents (endothelin and thromboxane A2). These changes are accompanied by decreases in cytoprotective substances including nitric oxide and prostacyclin, among others.

Although the intestinal tissue is very sensitive to ischemia it has a great epithelial regeneration capacity. During cold ischemia a separation of the epithelial surface from the lamina propria can occur, which is oedematous and often without inflammatory infiltration. During the revascularisation there are regenerative changes of the epithelium crypts with evident mitosis, capillary congestion, reduction in size of the villi and varying degrees of inflammatory infiltrate. These histological changes can last for 1 week after the transplant.

In a 2010 review that highlighted as a key factor the composition of the solution used and management for preservation specifically of the small intestine, the following characteristics stand out: low viscosity to facilitate blood washing, the presence of amino acids to improve viability and impermeability, colloids to prevent oedema, and maintaining pH homoeostasis. The most effective composition of the luminal solution and its clinical technique has not yet been achieved. Therefore, the preservation luminal solution and its technique need further research in transplant models to ultimately meet the physiological demands of graft during conservation[26].

Acute rejection

The incidence of rejection is >50% and usually appears after the first week, with a maximum risk during the first few months. Clinically, it can be completely silent if an early diagnosis is made. Symptoms such as bloating, abdominal

pain, diarrhoea or fever present. Cases of severe rejection can include a paralytic ileus, bleeding from desquamation of the mucosal and sepsis by bacterial translocation.

Chronic rejection

Chronic rejection has an incidence of 8-15%. Risk factors include the following: *a)* isolated bowel transplant regarding the combined transplant; *b)* the presence of acute rejection during the first month; *c)* older age of receptors, and *d)* being non-caucasian.

Clinical symptoms are nonspecific and produce a picture of chronic malabsorption. The suspected diagnosis is made by mesenteric arteriography, endoscopic biopsy and alteration of d-xylose test.

Infections

Infections are the most frequent causes of graft loss and death. Multiple factors can contribute to bacterial translocation: haemorrhagic *shock,* intestinal obstruction, high immunosuppression, total parenteral nutrition, antibiotic therapy, surgery itself, graft ischemia, ischemia-reperfusion injury, lack of continuity in the lymphatic system, venous drainage problems and, the most common, rejection.Cytomegalovirus infection is one of the most common infections, as is Epstein-Barr virus[27].

Graft-versus-host disease

Solid organ transplant probably has a higher incidence of graft-versus-host disease (5-14%) in recipients. The high immunosuppression they receive makes them very vulnerable to immune attack of mature lymphoid cells transmitted by the graft, resulting in graft versus host disease[27].

The clinic consists of diarrhoea, fever, dermatitis, onset of lymphadenopathy, liver dysfunction with haepatosplenomegaly (in cases of isolated intestinal transplant), medullary aplasia, etc.

Lymphoproliferative disease

Post-transplant lymphoproliferative disease has always been a serious complication in intestinal transplant[28], which often occurs ~25 months after transplant, but its precursors may occur long before lymphoproliferative disease[28].

International statistics on the activity of intestinal transplant

In 1985 the Intestinal Transplant Registry (ITR) was established whose mission is to provide data to the international community on the results of intestinal transplant in order to improve results and support efforts and policy making[29].

According to the data presented in Brussels at the IX International Symposium on Intestinal Transplant in June 2005, it is estimated that there was a total of 1,292 intestinal transplants in 1,210 patients worldwide. In most cases they are isolated intestinal transplant cases, but there have also been combined liver and intestine and multivisceral transplants. It was announced at the meeting held in Santa Monica, California that as of July 2007, 69 centres had registered and 28 (40.6%) reported activity during the 2005-2007 period. The total number of transplants reported from the beginning of the record is 1,720 conducted in 1,608 patients (746 isolated bowel transplants, 594 combined intestine and liver transplants, 380 multivisceral transplants). From2005-2007, 389 transplants were carried out worldwide, of which 301 patients were still alive when the report was published, evidencing the improvement in survival of both patient and graft.

In 2009, the ITR reported a total of 2,188 intestinal transplants performed in 73 registered centres worldwide. In September 2011, during the closing session of the XII International Symposium on Intestinal Transplantation, David Grant presented the report of the last registry, reporting that today the world has 79 registered centres, of which only 35 actively perform intestinal transplant. A total of 2,611 transplants have been carried out: 44% isolated, 2% combined liver-intestine and 24% multivisceral transplants. Graft survival has improved when analysing the 2006-2011 period (60% at 3 years). Patient survival at 10 years for isolated intestinal grafts and combined liver-intestine grafts was 46 and 42%, respectively. Graft survival for the same period was 29 and 39%, respectively. These results are comparable to the survival of patients who have undergone lung and heart transplants or pancreatic graft survival. During the past 2 decades, transplant centres have focused on improving short-term patient survival to an increase of >20%[29].

In Mexico there is a transplant centre registered with the Intestinal Transplant Association (ITA) in Torreon Coahuila; however, this centre is inactive.

In 2011, national newspapers, as well as the Speciality Medical Centre Puerta de Hierro in Guadalajara, Jalisco, reported the successful intestinal transplant of a living donor related to a 20-year-old with complete resection of jejunum and ileum by Dr. Federico Mendoza Sánchez, the first successful intestinal transplant in Mexico.

Currently, the National Transplant Centre (CENTRA) does not release statistics or registration of intestinal transplant or their waiting list.

Overview of immunosuppressive treatment

Currently, immunosuppression therapy is personalised according to patient characteristics as well as monitoring of rejection or infection.

Results obtained through the ITR have shown the usefulness of induction therapy, i.e., the administration of antilymphocyte monoclonal or polyclonal antibodies in a short period, during the procedure and immediately post-transplant. This initial aggressive therapy seeks to reduce host immune response to the graft, inducing the effect of conditioning on the receptor, depleting its lymphocyte load in addition to providing a therapeutic window for the progressive introduction of calcineurin inhibitors (tacrolimus)[30].

Over time, all available monoclonal antibodies have been used by different programmes; however, recent reports from this registry have stated that the use of induction with anti-interleukin 2 antibodies, antithymocyte or antilympho-

cyte improved graft and patient survival. Maintenance therapy has been recommended since the 1990s with a medication that in 1996 improved the survival rate in 1 year for isolated intestinal transplant from 17 to 65% compared with cyclosporine-treated recipients. The introduction of induction therapy allowed the use of (highly nephrotoxic) intravenous tacrolimus to be discontinued, instead using enteral treatment immediately post-transplant. The values sought during the first month of the post-transplant period are 15-20 ng/ml and to then reduce them to ~5 ng/ml at the end of the first year. Although this drug has provided great benefits, adverse effects should also be carefully monitored, with progressive renal dysfunction a cause of increased morbidity and higher than in other solid organs transplanted[30].

Corticosteroids are still used as part of maintenance therapy. Reports have recently begun to emerge where patients have discontinued them during the early or later post-transplant period, but further monitoring is needed to demonstrate the utility of the discontinuance. Sirolimus is another medication used for maintenance along with tacrolimus and has shown favourable results, which led to its use throughout various centres as it reached survivals rates in isolated intestine transplant at the end of the first year of 92%. Administration is recommended from the sixth post-transplant day due to the effect observed in delayed healing and for a variable time during the first year. The discontinuation rate due to adverse effects (neutropenia, viral infections and post-transplant lymphoproliferative syndrome) is 60%[30-32].

It is noteworthy that the treatment of rejection episodes should be aggressive because evolution from mild to severe rejection can be very rapid if not well monitored. The development of severe rejection causes not only graft loss, but mortality for the receptor. Its management requires experience because the loss of the mucosal barrier leads to bacterial translocation and sepsis, only improving as the mucosal barrier recovers. Aggressive immunosuppressive therapy and adequate antibiotic coverage during this treatment are needed. Steroid-resistant moderate and severe rejections require 7 to 14 days treatment with antilymphocyte antibodies. In cases of refractory rejection, incorporation of sirolimus has been proposed and there are some publications in favour of using infliximab, anti-tumour necrosis factor monoclonal antibody-α. According to the Pittsburgh group, 8% of patients suffer chronic rejection, which usually manifests with progressive development of II parallel to villous atrophy in biopsies and is a cause of loss far from the graft, especially in patients who have undergone isolated bowel transplant[32].

Monitoring graft survival

Immunology

Research tests demonstrate the clinical utility in intestinal transplant recipients when the following markers are included:

- First, flow cytometry to measure the response of mixed leukocytes, which detect the donor proliferation induced by receptors of cytotoxic T cells by ester-succinimidyl carboxyfluorescein dye dilution or CD154 expression in receptor memory cytotoxic T cells. Among these tests, CD154+ memory cytotoxic T cells are known to achieve maximum sensitivity and specificity, at least 90%, in detecting acute cellular rejection.
- Second, elevated faecal calprotectin, a marker for early detection of intestinal inflammation, which may indicate the need for a biopsy, especially after the closure of the stoma ileostomy.
- Third, nucleotide polymorphisms associated with inflammatory bowel diseases; for example, nucleotide-binding oligomerisation protein, type 1 stimulated macrophages. These single nucleotide polymorphisms can be used, as shown by several studies, to select a receptor who is prone to intestinal transplant rejection in order to manage them with more powerful immunosuppression.

Biopsy

Intestinal graft monitoring is considered to be unique, as signs of acute cellular rejection are visible through endoscopy. Currently there are endoscopic criteria to detect graft rejection as well as endoscopic monitoring protocols.

The main locations for biopsy are the entire ileum or the jejunum. Macroscopic features that lead to suspecting rejection are alterations of *a)* villus height; *b)* mucosal motility; *c)* end of the villi; *d) background* erythema *f)* bleeding of the villous; *g)* friability of tissue.

The first post-perfusion biopsy should be performed at the time of transplant, 3-5 days after transplantation, then weekly for 1 month, every 2 weeks for the following 2 months and monthly during the next 6-12 months until the stoma is closed.

Intestinal transplant: international experience over time

Benedetti et al.[33] published the experiences of a centre in Chicago from April 1998 to October 2004 where 12 living donor transplants were performed on 11 patients (seven males and four females, with an average age of 26 years). In adults, the graft was a 200-cm length of intestine with immune therapy support. In general, patient survival at 3 years was 82%, with a graft survival of 75%. In the last eight transplant patients after January 2000, patient and graft survival at 1 year was 100 and 88%, respectively. The average hospital stay was 36 days (range 13-290 days).

Meneu et al.[16] released the first series of intestinal transplant in adult recipients in Madrid in 2006. They presented their experience in the evaluation of 20 potential candidates for intestinal transplant between June 2004 and October 2005. Five transplants in four patients (two retransplant, two desmoid tumours and one short bowel syndrome after excision by mesenteric ischemia) were performed. At the end of the study and after a follow-up with an average of 180 days (range 90-190 days), all the receptors and 75% of the grafts survived.

In 2010 Mazariegos et al.[34] published a series of intestinal transplant cases in the United States between 1999 and

2008 that included 700 post-transplant patients. Patient and graft survival at 1 year was 89 and 79% for isolated bowel transplant, and 72 and 69% in the hepatointestinal transplant, respectively. At 10 years the patient and graft survival decreased to 46 and 29% for isolated bowel transplant and 42% and 39% for hepatointestinal transplant, respectively[34].

The current experience of intestinal transplant in Japan was reported by Ueno et al.[35] between 1996 and 2011. There were 17 intestinal transplants and 11 of those were from living donors. The reported 5-year overall survival rate was 69% for patients and 60% for grafts. A lack of national health coverage and the limit on the number of cadaveric donors were the two main reasons Japan initiatedthe living donor experience[35].

Conclusion

Intestinal transplant today remains a challenge for the scientific medical community, but progress in clinical research and surgical and immunological, etc. areas continues to be made. It is clear that the research field is wide and that there is an interest in solving current problems. Without a doubt, the time for intestinal transplant as the treatment of choice for intestinal failure is getting closer.

Conflict of interest

The authors declare no conflict of interest.

Bibliography

1. Rodríguez A, Cánovas G. Síndrome de intestino corto en adultos. Tratamiento nutricional. Endocrinol Nutr. 2004;51(4):163-72.
2. Ballesteros P, Vidal A. Síndrome de intestino corto: definición, causas, adaptación intestinal y sobrecrecimiento bacteriano. Nutr Hosp. 2007;22(Suppl 2):74-85.
3. Martínez M, Fabeiro M, Dalieri M, Barcellandi P, Prozzi M, Hernández J, et al. Evolución y sobrevida de pacientes pediátricos con síndrome de intestino corto (SIC). Nutr Hosp. 2011;26(1):239-42.
4. Sachin A, Cleo P, Hari I, Akhil M. Short bowel syndrome in the NICU. Clin Perinatol. 2013;40:53-68.
5. Sukhotnik I, Siplovich L, Shiloni E, Mor-Vaknin N, Harmon C, Coran A. Intestinal adaptation in short-bowel syndrome in infants and children: a collective review. Pediatr Surg Int. 2002;18(4):258-63.
6. Thompson J, Weseman R, Rochling F, Mercer D. Current management of the short bowel syndrome. Surg Clin North Am. 2011;91(3):493-510.
7. Javid P, Sanchez S, Horslen S, Healey P. Intestinal lengthening and nutritional outcomes in children with short bowel syndrome. Am J Surg. 2013;205(5):576-80.
8. López R, Morenob A, Ramos B, Martínez-Ojinaga N, Hernanz M, Bozanoa B, et al. Valor de la citrulina plasmática como biomarcador de función intestinal en el síndrome de intestino corto y en el trasplante intestinal. An Pediatr Barcelona. 2013;79(4):218-23.
9. De Cos A, Gómez C, Vázquez C, López S, Vicente E; Grupo NADYA-SENPE. Trasplante intestinal en el paciente con nutrición parenteral domiciliaria. Nutr Hosp. 2003;18(6):325-30.
10. Naimi R, Madsen K, Askov-Hansen C, Brant C, Hartmann B, Holst J, et al. A dose-equivalent comparison of the effects of continuous subcutaneous glucagon-like peptide 2 (GLP-2) infusions versus meal related GLP-2 injections in the treatment of short bowel syndrome (SBS) patients. Regulatory Peptides. 2013;184;47-53.
11. Madsen K, Askov-Hansen C, Naimi R. Acute effects of continuous infusions of glucagon-like peptide (GLP)-1, GLP-2 and the combination (GLP-1 + GLP-2) on intestinal absorption in short bowel syndrome (SBS) patients. A placebo-controlled study. Regul Pept. 2013;184:30-9.
12. Fitzgibbons S, Ching YA, Valim C, Zhoua J, Iglesias J, Duggan C, et al. Relationship between serum citrulline levels and progression to parenteral nutrition independence in children with short bowel syndrome. J Pediatr Surg. 2009;44(5):928-32.
13. Lillehei RC, Goott B, Miller FA. The psychological response of the small bowel of the dog to ischemia including prolonged in vitro preservation of the bowel with successful replacement and survival. Ann Surg. 1959;150(4):543-560.
14. Toledo-Pereyra LH, Sutherland DE. Richard Carlton Lillehei transplant and shock surgical pioneer. J Invest Surg. 2011;24(2):49-52.
15. Watson AJ, Lear PA. Current status of intestinal transplantation. Gut. 1989;30(12):1771-82.
16. Meneu Díaz JC, Moreno González JI, García García JI, Moreno A, Montejo JC, Colina F, et al. Primera serie nacional de trasplante de intestino en receptores adultos. Rev Esp Enferm Dig. 2006;98(10):723-39.
17. Gondolesi GE, Rumbo C, Fernández A, Mauriño E, Ruf A. Trasplante intestinal. Revisión y descripción de su evolución en Latinoamérica. Acta Gastroenterológica Latinoamericana. 2009;39(1):63-80.
18. Vianna RM, Magnus RS. Present prospects and future perspectives of intestinal and multivisceral transplantation. Curr Opin Clin Nutr Metab Care. 2009;12(3):281-6.
19. American Gastroenterological Association medical position statement: short bowel syndrome and intestinal transplantation. Gastroenterology. 2003;124(4):1105-10.
20. Argibya P, Ceballos M. Trasplante de intestino delgado. Cir Digestiva. 2009;259(2):1-13.
21. Lépez M, Hernández M. Indicaciones, técnicas y resultados del trasplante de intestino delgado. Nutr Hosp. 2007;22(2):113-23.
22. Tzakis A, Kato T, Levi D, Defaria W, Selvaggi G, Weppler D, et al. 100 multivisceral transplants at a single center. Ann Surg. 2005;242(4):480-90.
23. Matsumoto C, Fishbein T. Modified multivisceral transplantation with splenopancreatic preservation. Transplantation. 2007;83(2):234-6.
24. Garg M, Jones R, Vaughan R, Testro A. Intestinal transplantation: Current status and future directions. J Gastroenterol Hepatol. 2011;26(8):1221-8.
25. Montalvo-Javé E, Tattersfield T, Ortega J. Factors in the pathophysiology of the liver ischemia-reperfusion injury. J Surg Res. 2008;147(1):153-9.
26. Roskott A, Nieuwenhuijs V, Dijkstra G, Koudstaal L, Leuvenink H, Ploeg R. Small bowel preservation for intestinal transplantation: a review. Transpl Int. 2011;24:107-31.
27. Ruiz P, Kato T, Tzalkis A. Current status of transplantation of small intestine. Transplantation. 2007;83(1):1-6.
28. Abu-Elmagd K, Zak M, Stamos J, Bond G, Jain A, Youk A, et al. De novo malignancies after intestinal and multivisceral transplantation. Transplantation. 2004;77(11):1719.
29. Golodesi G, Gondolesi G, Almau H. Intestinal transplantation outcomes. Mt Sinai J Med. 2012;79(2):246-55.
30. Ojo A. Renal desease in recipients of nonrenal solid organ transplantation. Semin Nephrol. 2007;27(4):498-507.
31. Fryer J. Intestinal transplantation: current status. Gastroenterol Clin North Am. 2007;36(1):145-59.

32. Fishbein T, Florman S, Gondolesi G, Schiano T, LeLeiko N, Tschernia A, et al. Intestinal transplantation before and after the introduction of sirolimus. Transplantation. 2002;73(10):1538-42.
33. Benedetti E, Holterman M, Asolati M, Di Domenico S, Oberholzer J, Sankary H, et al. Living Related Segmental Bowel Transplantation: From Experimental to Standardized Procedure. Ann Surg. 2006;244(5):694-9.
34. Mazariegos G, Steffick D, Horslen S, Farmer D, Fryer J, Grant D, et al. Intestine transplantation in the United States, 1999-2008. Am J Transpl. 2010;10(Part 2):1020-34.
35. Ueno T, Wada M, Hoshino K, Yonekawa Y, Fukuzawa M. Current status of intestinal transplantation in Japan. Transpl Proc. 2011;43(6):2405-7.