

Intestinal and multivisceral transplantation

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Abstract

Intestinal and multivisceral transplantation represents an important treatment option for patients with intestinal failure. Early attempts were hindered by technical and immunological complications. However, significant developments in immunosuppressive therapy have led to marked improvements in outcomes in recent years. The main indications for intestinal transplantation are life-threatening complications or unacceptable quality of life on total parenteral nutrition (TPN), or following evisceration for extensive intra-abdominal tumours. In suitable patients, in the absence of significant liver disease, an isolated intestinal graft is appropriate. A combined liver and intestinal transplant is indicated in patients with significant liver disease, almost always as a result of long-term TPN. Pathology affecting the foregut may require more extensive grafts including the stomach, duodenum and pancreas. Multivisceral transplantation is technically demanding. The transplant recipient has frequently undergone multiple previous laparotomies and may present with multiple stomata, fistulae, collections, distortion of intra-abdominal anatomy and significant contraction of the abdominal cavity. The most important early complications are acute rejection and sepsis, which frequently occur together. In the long-term, chronic rejection and malignancy are the leading causes of graft loss and mortality and immunosuppression related renal impairment a major source of morbidity. It is hoped that ongoing improvements in intestinal and multivisceral transplantation may eventually justify its use as a primary alternative to long-term TPN.

Keywords Intestinal transplantation; multivisceral transplantation

History and introduction

The first human intestinal transplant was a short segment of duodenum as part of a pancreatic graft performed in 1966 at the University of Minnesota by Lillehei et al.¹ The same group concurrently reported a graft combining stomach, pancreas and intestine in a patient with mesenteric thrombosis, which similarly to many subsequent attempts over the next 20 years, failed to achieve long-term survival. It was not until 1988 that the first long-term success was reported with a combined liver and intestinal graft.² This represented a watershed, as the results of intestinal and multivisceral transplantation gradually improved through the 1990s. Technical developments contributed in part to the observed improvements, but these were predominantly related to progress in immunosuppressive therapy, first with the

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introduction of ciclosporin-based regimens but more importantly with the widespread use of tacrolimus and lymphocyte depleting induction agents, such as alemtuzumab.³ In 1996 an International Intestinal Registry was established and reported a worldwide total of 180 transplants performed at 25 centres.⁴ The expansion of intestinal transplantation programmes has been such that this figure now approaches 3000 transplants. Having peaked at approximately 150 cases per year worldwide, activity has decreased recently with the introduction of improved intestinal rehabilitation programmes offering an alternative predominantly for the paediatric population⁵ but the number of intestinal and multivisceral grafts being performed annually is still in the region of 120 cases.

Indications

Intestinal transplantation represents an alternative therapeutic option for patients with short bowel syndrome (SBS) dependent on long-term parenteral nutritional support. Transplantation has been performed for most causes of SBS whether secondary to functional deficiency or physical depletion due to massive or repeated surgical resection. Gastroschisis, volvulus, necrotizing enterocolitis and pseudo-obstruction are the most common underlying causes in paediatric practice. In adult intestinal transplantation, the most common causes of SBS are mesenteric vascular disease, Crohn's disease, trauma, dysmotility disorders and desmoids tumours. The general viewpoint is that the procedure is not currently justified in patients who remain stable on total parenteral nutrition (TPN) without any significant TPN-related complications who have a good life expectancy without transplantation. However, in patients who do develop life-threatening complications, predominantly recurrent line sepsis or TPN-related liver disease, or run out of sites for venous access, intestinal transplantation has a clearly defined role. Intestinal transplantation may also be considered in very carefully selected patients reporting intolerably poor quality of life on TPN, despite the possibility of diminished long-term survival (Box 1).

In suitable patients with SBS, in the absence of significant liver disease, an isolated intestinal graft is appropriate and usually comprises the small bowel alone. A combined liver and intestinal transplant is indicated in patients with intestinal failure in the presence of significant liver disease, commonly arising as a result of long-term TPN. Historically this situation was

Indications for intestinal and multivisceral transplantation

- Life-threatening complications of TPN
 - Severe or progressive liver disease
 - Life-threatening line infection or recurrent fungal line infection
 - Lack of central venous access
 - for isolated bowel graft: access limited to three major sites
 - for intestinal as part of multivisceral graft: access limited to four sites
- Very poor quality of life on TPN thought to be correctable with transplantation
- Patients undergoing extensive surgery involving partial or complete evisceration

Box 1

significantly more common in paediatric patients due to the increased sensitivity of small children to the hepatotoxic effects of parenteral feeding.⁶ Establishing the extent and, most importantly, potential reversibility of TPN-related liver injury, and therefore the need to include a liver in the graft, remains a difficult matter of clinical judgement. In recent years, there have been great advances in the management of children with short bowel syndrome. Refinement in the management of TPN has in part led to a reduction in the incidence of secondary liver disease but, more importantly, the development of successful intestinal rehabilitation programmes have allowed many children to return to full enteral nutrition avoiding the need for either long-term parenteral nutrition or intestinal transplantation.⁵ In this context, surgical bowel lengthening procedures such as the Bianchi or STEP procedures offer an important additional avenue for these paediatric cases.⁷

Full multivisceral grafts including the stomach, duodenum and pancreas in addition to the liver and small bowel are occasionally indicated in the absence of significant parenchymal liver disease, for example, in the context of coeliac trunk vascular disease at high risk of occlusion and previous intestinal infarction. A developing indication is in the case of patients with end-stage liver disease complicated by mesenteric venous occlusion where conventional liver transplantation is not an option in the absence of any source of portal inflow to the grafted liver but where a multivisceral graft offers the opportunity of restoring normal anatomy and function. Multivisceral grafting can also provide a primary option in management of large 'benign' intra-abdominal tumours, such as desmoid tumours, where resection can require excision of most, if not all, the intra-abdominal organs.⁸ Attempts to extend the concept to allow ultra-radical excision of advanced midgut based malignancies appeared initially promising⁹ but were abandoned as the prohibitively high recurrence rate became apparent.

Pre-operative assessment

Patients being considered for multivisceral or intestinal transplantation usually require a period of in-patient assessment and optimization at an intestinal failure/transplant unit. Multivisceral transplantation is the archetypal multidisciplinary speciality and initial input from surgeons, gastroenterologists, hepatologists, radiologists, anaesthetists, specialist nurses in gastroenterology and transplantation, dieticians, pharmacists, physiotherapists, occupational therapists, tissue typists and psychologists will be required. The transplant team must assess the patient's suitability for transplantation in great detail, including anatomical and technical considerations, physiological function and reserve, immunological factors and psychological issues, in particular pain and drug dependence that are common in this patient population. Optimization aims to improve fitness for major surgery and the complicated and prolonged postoperative period, particularly in regard to cardiorespiratory function and nutritional status. In addition, identification and effective treatment of ongoing sepsis is crucial and may require significant intervention, including repeated surgery.

Adequate vascular access in patients with a history of long-term TPN is a major problem in planning intestinal transplantation. Indeed, patients relying on femoral access due to loss

of neck veins may become untransplantable, as access above the hepatic veins is essential for multivisceral transplantation. The key factor influencing vascular access, and indeed general optimization of the patient, is timely referral to an intestinal transplant centre.¹⁰ Prompt referral is also crucial in patients with TPN-related liver disease as transplantation prior to development of irreversible changes may permit isolated small bowel transplantation, avoiding the need for more complicated grafts and leaving the other scarce donor organs for further transplant recipients. This may also offer the recipient of an isolated intestinal graft the option of graft removal and return to TPN in the face of life-threatening complications such as severe refractory acute rejection, an option not open to the recipient of a multivisceral graft if further organs are not available for immediate retransplantation. The timing of referral may need to be much earlier than generally perceived by referring centres as the availability of suitable donors is still problematic and intestinal transplant patients frequently remain on the waiting list for prolonged periods, which is associated with a higher waiting list mortality rate than for any other solid organ.¹¹

Adequate imaging is essential prior to consideration for transplantation. A detailed 'map' of the surgical field in regard to the extent of remnant bowel and the presence of fistulae and collections must be obtained. In addition, thorough imaging of the arterial, venous and portal intra-abdominal vasculature, is crucial for planning implantation. This is achieved with a combination of imaging modalities including computed tomography (\pm angiography), magnetic resonance imaging (in particular MR enteroclysis and venography), digital subtraction angiography, barium studies and fistulography. A careful assessment of organ function may also be required, for example measurement of glomerular filtration rate in the context of chronic renal impairment if consideration is being given to the addition of a renal transplant to a multivisceral graft.

Surgical technique

The four basic types of intestinal transplant are small bowel alone, liver and small bowel, multivisceral (most commonly combining liver, stomach, duodenum, pancreas and small bowel) and modified multivisceral (a multivisceral graft excluding the liver). However, most combinations of intra-abdominal organs can be transplanted. Inclusion of a renal allograft in multivisceral grafts for recipients with end-stage chronic renal failure as part of their presentation is widely reported. One centre has advocated routine inclusion of the spleen in multivisceral grafts to prevent infection related to asplenia and potentially reduce the risk of rejection.¹² However, this remains contentious, as there is a perceived increased risk of graft versus host disease associated with splenic inclusion. The colon was included in some early intestinal transplants but there were diagnostic difficulties with a high incidence of discordant normal colonic biopsies in the face of small bowel rejection. Despite these difficulties there is a resurgence of interest in inclusion of at least a segment of colon with the ileocaecal valve in the graft because of the improved management of fluid balance achieved by doing so. The vast majority of grafts are from donors following brainstem death but successful live donor isolated small bowel transplantation has been performed.¹³

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