Recent developments in transplantation of the small intestine

A S Soin and PJ Friend
Department of Surgery, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

The widespread application of intestinal transplantation depends upon achieving a success rate sufficiently high to warrant treating patients by transplantation rather than parenteral nutrition. This is analogous to the situation in renal transplantation (where the alternative is dialysis) and pancreatic transplantation (insulin treatment) and contrasts with the situation in liver and heart transplantation where there is no effective alternative therapy. The main barrier to success at this level is immunological; progress will depend on improved prevention, diagnosis and treatment of rejection. Although developments are expected of new and more potent immunosuppressive drugs, it is possible that acceptable long-term results will require a more fundamental manipulation of the immune response in order to achieve at least partial tolerance of the graft.

Intestinal failure is defined as the loss of intestinal absorptive function to such an extent as to necessitate parenteral nutritional support. This occurs as a consequence of many conditions, most commonly mesenteric infarction (often secondary to thrombotic disorders), Crohn’s disease, desmoid tumours and trauma in adults, and gastroschisis, congenital atresia, necrotising enterocolitis, volvulus and motility disorders in children.

Parenteral nutrition

Until recently, survival of patients with irreversible intestinal failure required life-long support with parenteral nutrition. At present, of the order of 300 patients are maintained on home parenteral nutrition in the UK (M. Elia, personal communication). This treatment is effective as measured by survival—3 year patient survival is around 75%². However, this is not an ideal therapy for several reasons, and is extremely expensive, with annual recurrent costs of approximately £50,000.

Long-term parenteral nutrition is associated with significant morbidity for a number of reasons. Patients are at risk of cholestatic liver disease; this is a particular problem in children and may progress to chronic liver
disease. Other major limitations include sepsis related to long-term venous cannulation and venous thrombosis often involving major veins in the neck. When this occurs, the provision of vascular access may become a critical factor.

Quality of life is markedly impaired in many patients. Successful long-term parenteral nutrition requires very close adherence to a rigorous protocol in order to maintain optimal nutrition and, most importantly, to prevent infection of the venous access site. This restricts the activities of the individual considerably, although well-motivated patients do adapt to a remarkable degree. The requirement for patient involvement in the treatment is considerable and much of the improvement in longer term results is due to training of the patient in management of the venous access site; meticulous attention and technique has reduced considerably the incidence of catheter-related complications. Many patients are less capable and problems occur early and frequently.

**Intestinal transplantation**

Successful intestinal transplantation should prevent all the medical problems of parenteral nutrition and achieve good quality of life. However, the cost of this to the patient is the morbidity and mortality of the procedure and the requirement for life-long immunosuppression.

Despite this apparent role for intestinal transplantation, the clinical development of this therapy has occurred slowly and considerably later than that of the related techniques of kidney, liver, heart and lung transplantation. This is not because the surgical aspects of intestinal transplantation are more difficult to surmount but, mainly, because of immunological limitations. Not only is the mucosa of the intestine rejected aggressively, but the immediate consequences of rejection are severe; damage to the mucosa leads to loss of the barrier to translocation of bacteria from within the lumen of the bowel. Thus, rejection is followed shortly by bacterial translocation and septicaemia. At this stage, appropriate treatment for rejection (high dose immunosuppression) is relatively contra-indicated by the presence of sepsis. In order to reduce the consequences of rejection and translocation, selective bowel decontamination has been used (enteral treatment with non-absorbable antibiotics), although no benefit has yet been demonstrated using this strategy.
Prevention of rejection

The most apparent solution to this problem is effective and reliable prevention rather than treatment of rejection. However, it has not been possible to achieve this level of immunosuppression using the drugs which have been available, both because of the non-specific nature of the immunosuppression produced (and the associated side-effects of over-immunosuppression) and the other toxic effects of the principal drugs (particularly nephrotoxicity and neurotoxicity of cyclosporin).

Intestinal transplantation has recently become a practical proposition; this is for two main reasons, both related to prevention of rejection. It has been recognised for many years that transplantation of the liver confers an immunological advantage to other organs transplanted from the same donor. The mechanism by which this occurs is not fully understood or agreed, but a factor present in serum appears to be important in this phenomenon. It has been suggested that soluble MHC Class I antigen is the critical factor; it is known that donor type MHC Class I is present in the serum of transplanted patients within minutes or hours of reperfusion of the graft. Alternatively, the establishment of donor lymphoid cells in the tissues of the recipient may be important. This is known to occur, although whether it is responsible for the 'liver effect' is not proven. This effect, however, does appear to be of clinical significance; the incidence of renal allograft rejection is lower in patients who receive a combined kidney and liver transplant than in recipients of kidney allografts alone. The first successful series of intestinal transplantation was reported by Grant et al. and took advantage of this phenomenon; all the patients in this series received combined liver and small intestinal transplants and were treated with a cyclosporine-based immunosuppressive regimen.

The second factor in the recent resurgence of interest in intestinal transplantation is the development of new immunosuppressive drugs with a higher therapeutic index than conventional agents. The use of FK506 (tacrolimus) has enabled the successful transplantation of intestinal grafts without the liver. More recently, other novel drugs have become available. Mycophenolate mofetil has been shown to reduce the incidence of rejection following renal transplantation and it is hoped that the addition of this agent will enhance the benefit already established with tacrolimus.

Another problem which was predicted to complicate intestinal transplantation is graft-versus-host disease. The small intestine and its mesentery contain a very large mass of lymphoid tissue which, if transplanted in a viable form, might be expected to recognise as foreign and attack the tissues of the host. Experimental studies in rodent models have confirmed that lethal graft-versus-host disease occurs following...
intestinal transplantation between appropriate strain combinations. Graft-versus-host disease is a major cause of morbidity and mortality in bone marrow transplantation and has also been recognised as a much less frequent cause of morbidity after liver transplantation. Some initial clinical protocols, therefore, included strategies to reduce the mass or viability of the transplanted lymphoid tissue, including pretreatment of the donor with anti-thymocyte globulin. However, although circulating lymphocytes of donor origin have been identified, the risk of significant disease appears to be extremely small and preventative measures are not currently considered necessary. The reason for this discrepancy between the experimental evidence and clinical practice is not fully understood.

A further immunologically-based complication of intestinal transplantation is the development of post-transplant lymphoproliferative disorder (PTLD). This is a well-recognised complication of organ transplantation and is frequently associated with infection by Epstein-Barr virus. The risk of developing PTLD appears to be related to the intensity of immunosuppression used, particularly the use of anti-lymphocyte antibody preparations. The very high incidence of PTLD reported after intestinal transplantation may be a function of the large lymphoid cell population of the graft or of the very heavy immunosuppression which is needed in this group of patients. PTLD may resolve spontaneously if immunosuppression is stopped, this requiring removal of the graft, but is fatal in many cases.

Which patients?

Because of the problems associated with transplantation, it is generally agreed that this should be recommended for those patients who are developing serious complications of parenteral nutrition, rather than all patients who are on long-term parenteral nutrition. The complications which would be regarded as relative indications for transplantation include the development of cholestatic liver disease and recurrent problems with vascular access (sepsis and/or venous thrombosis). In some patients, intractable abdominal pain may complicate the abdominal pathology and constitute a relative indication. In a small number of patients, intestinal transplantation may be carried out as part of a planned procedure for intestinal or mesenteric tumour, whereby the tumour is removed with the intestine, the patient stabilised on parenteral nutrition and transplantation carried out at a later date. In those cases in which the liver and/or other abdominal visceral are involved and a more extensive resection is needed, there may be an indication for removal of the tumour and transplantation as a single procedure.
Transplantation of the small intestine

Techniques

Intestinal transplantation may involve transplantation of the small intestine alone or with the right colon. It may be combined with liver transplantation (liver–small intestine) or combined with transplantation of two or more other abdominal viscera (multi-visceral transplantation). The donor for an intestinal allograft (alone) may be a brain-dead cadaver or a living donor. Whereas the cadaveric graft usually consists of the entire small intestine with or without the ileo-caecal junction and a variable portion of the right colon, a graft from a living donor is 5–6 feet of proximal or distal small bowel based on the respective branches and tributaries of the superior mesenteric artery and vein. The longer the length of the small bowel graft, the more complete is the recovery of absorptive function. However, successfully transplanted partial small bowel grafts (from living donors) have now been shown to provide sufficient absorptive function to allow existence free of parenteral nutrition. Although partial intestinal graft transplantation has the theoretical advantage of carrying less lymphoid tissue load, no convincing clinical advantage has yet been shown. While transplantation of distal ileum is technically easier than proximal small bowel and has the advantage of better adaptation capacity of the ileum, its removal is more likely to result in malabsorption in the donor. However, this has not been a significant cause of morbidity in donors in the very limited experience with this procedure. Although inclusion of ileo-caecal junction and right colon may improve vitamin $B_{12}$, bile salt and water absorption, this procedure is not currently favoured. Any functional gain is offset by the increased load of lymphoid tissue and microbes that it entails, resulting in a higher incidence of bacterial translocation, infection and GVHD.

Transplantation is carried out by anastomosing the superior mesenteric artery to the recipient aorta and the superior mesenteric or portal vein to either the inferior vena cava or the recipient portal vein. The theoretical physiological advantage of portal venous drainage has not been proven and hence the simpler caval drainage is usually performed. The ends of the graft are anastomosed to the recipient intestine, proximally and distally. The distal portion of the transplanted bowel is brought out as a loop stoma or end-stoma with a side-to-end anastomosis between the donor small intestine and the recipient large intestine. This enables periodic histological monitoring of the graft for rejection. If the distal bowel in the recipient is otherwise normal, the stoma is closed after 6–12 months.

Transplantation of the liver and small intestine is carried out as a single block with the small intestine attached to the liver by the portal vein. Drainage of the residual recipient splanchnic circulation is usually
Transplantation achieved by anastomosis of the recipient portal vein to the side of the donor portal vein. Arterial reconstruction is performed by using a conduit of donor aorta containing the orifices of the superior mesenteric and coeliac arteries; this is anastomosed to the infra-renal aorta.

Multi-visceral transplantation includes at least three of the abdominal organs, liver, stomach, pancreas, small intestine, kidney. The techniques used for transplantation depend upon the details of the particular case, but usually include inferior vena caval anastomoses as in a liver transplant, an upper gastro-intestinal anastomosis and distal stoma (with or without anastomosis) and an arterial reconstruction involving an aortic conduit or interposition segment.

Experience gained

In the early days of transplantation, interest in the small intestine waned quickly due to the apparently insurmountable problems of rejection and sepsis. With the introduction of cyclosporin, there was a renewal of enthusiasm but, again, the results were disappointing, particularly for intestinal grafts in the absence of a liver graft. The development of tacrolimus resulted in a rapid expansion of intestinal transplantation in many units around the world. However, the experience since gained still suggests that rejection remains the limiting factor in the transplantation particularly of the intestine alone. Acute rejection is frequent and has serious implications, as described above. However, unlike transplantation of other solid organs, the risk of rejection appears to persist at a high level for a prolonged period after transplantation, possibly even indefinitely. In addition, it is becoming clear that chronic rejection can develop at any time, even years after transplantation. The use of other drugs in addition to tacrolimus may be effective; in particular, there is considerable interest in the use of mycophenolate which has been shown in trials in renal transplantation to reduce the incidence of rejection with a low level of toxicity. It is possible that the widespread application of intestinal transplantation to all patients in intestinal failure will need to await the development of an effective strategy for the induction of donor-specific tolerance. The approaches currently under investigation include immunomodulation with donor bone marrow infusion and/or short courses of monoclonal antibodies against lymphocytes or adhesion molecules.

Unlike other solid organ grafts, there is no specific biochemical marker to suggest rejection of an intestinal graft. Histology remains the gold standard for the diagnosis of rejection, although this method is far from ideal for several reasons. First, it necessitates either a stoma or regular
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doscopic examinations. Second, the histological features of rejection are initially non-specific and may be mimicked by surface trauma or infective enteritis. Third, the rejection is often patchy and the diagnosis may be missed. Since rejection increases intestinal permeability, tests of permeability, such as renal excretion of \[^{51}\text{Cr} \]-EDTA and \[^{14}\text{C} \]-mannitol 6 h after ingestion, may provide valuable indirect evidence of rejection\(^{20}\). There is evidence that rejection may cause changes in serum levels of nitroso compounds and tissue nitrous oxide synthase concentrations. However, it is not yet clear if these tests will be sensitive and specific enough to diagnose rejection.

The function of transplanted intestine recovers within weeks or months despite the fact the extrinsic innervation and lymphatic drainage are disrupted at the time of surgery. Division of lymphatics leads to long-chain fatty acid malabsorption and denervation may lead to intestinal dysmotility; these factors are associated with post-transplant diarrhoea. In order to encourage good enterocyte function, growth and adaptation, early introduction (within 2–3 weeks) of enteral nutrition is of paramount importance. In particular, the inclusion of glutamine in the diet has been shown to facilitate recovery of mucosal function\(^{21}\).

The data from intestinal transplantation cases are currently collated as an International Intestinal Transplant Registry and the results presented and published regularly. At the last update\(^1\), a total of 180 intestinal transplants had been reported. Approximately half of these were combined liver and small bowel grafts, 38% small bowel grafts alone, and 16% multivisceral grafts including intestine. The aetiology of intestinal failure included short gut syndrome, desmoid tumour, Crohn's disease, cancer, and villous atrophy. The two main reasons for including a liver graft were parenteral nutrition-induced liver disease and extensive portal venous thrombosis causing portal hypertension. Multivisceral grafts were usually carried out following partial or complete abdominal exenteration for locally invasive or malignant tumours. Most patients with non-malignant indications were transplanted because of complications of parenteral nutrition, particularly difficulties with intravenous access, sepsis and liver disease. A little over half of the patients were already in the hospital at the time of their transplant and one in six was already in an intensive care unit.

In most cases, cold ischaemia was restricted to a mean of 6 h, although grafts preserved for up to 16 h have been transplanted successfully. University of Wisconsin solution was used to preserve the grafts in most instances. Cyclosporin-based regimens were used in a quarter of these patients, predominantly in the early years of intestinal transplantation. The other patients received tacrolimus-based immunosuppression, a policy that has now become standard at most centres.
Although considerable short-term success has been achieved, results in the longer term remain disappointing. One and three year survivals of 59/32%, 59/40%, and 51/40% were reported for small bowel, combined liver and small bowel, and multivisceral grafts, respectively, using tacrolimus-based immunosuppression. It appears that if a combined liver/intestinal or multivisceral graft survives the initial postoperative period, it is more likely to survive in the long-term than an isolated intestinal graft. Tacrolimus based regimens were found to result in higher graft survival in all groups.

The most frequent causes of graft loss included rejection (33%), lymphoma (12%), cytomegalovirus infection (19%), graft thrombosis (4%), and death (69% – including those from above causes). Of the survivors, 78% had full function, 12% partial function and in 10% the graft had been removed. More than half of the patients who died had functioning grafts at the time of death. In the successful cases, the mean time to stopping parenteral nutrition was approximately 12 weeks after transplant.

References


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