Intestinal transplantation: living related

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The use of live donors in intestinal transplantation could potentially both reduce the severity of rejection responses against this highly immunogenic organ by better tissue matching and also reduce cold ischaemia times. These two advantages over cadaveric grafts could preserve mucosal integrity and reduce the risk of systemic sepsis from bacterial translocation. The disadvantages of live donation are the inherent risk to the donor and the compromise of using a shorter graft. Although only a handful of such cases have been performed, the success rate has been high and this is a therapeutic modality which should be explored further.

Clinical background

Small bowel transplantation is still in its infancy and is currently at the interface of experimental surgery and a proven clinical alternative. There were 8 reported attempts at intestinal transplantation made in the 1960s, in patients who had undergone massive small bowel resection. Of these, 5 used cadaveric grafts but 3 cases, performed in Boston, Mississippi and New York, used segmental transplants from live donors. In all cases the patients died, largely for two reasons: firstly, the immunosuppressive agents that were available at that time were not sufficiently powerful to overcome the fierce rejection which the transplanted intestine suffers; and secondly, the patients were transplanted immediately following massive bowel resection because there was no effective means of maintaining nutritional support in such patients while their clinical condition could be stabilised.

With the advent of total parenteral nutrition (TPN) in 1969, interest in small bowel transplantation, which had become considered as the ‘forbidden fruit’ of transplant surgeons was lost for nearly two decades.
The modern era

In 1988, Grant et al. performed the first case of successful cadaveric transplantation of a combined small bowel/liver graft in London, Ontario, Canada. That same year, Deltz described the first case of successful intestinal transplantation using a living donor. In this case, a 42 year old woman suffering from short gut syndrome received a 60 cm segmental graft from her half sister. This unit also performed a second case, in which a 5 year recipient received a graft from her mother but this graft was lost to rejection after 12 days.

The second case of successful allogeneic clinical intestinal transplantation from a live donor was performed in Leeds, UK, in February 1995. This case in many ways typifies the 'last resort' status of bowel transplantation in the clinical situation.

The patient was a 28 year old woman who had undergone total colectomy for Gardner's variant of familial adenomatous polyposis, but subsequently developed a desmoid tumour of the mesentery involving the superior mesenteric vessels. The tumour caused intestinal obstruction at multiple sites and intractable back pain from infiltration. Resection of the tumour was undertaken at a late stage, when the patient had already been referred to a hospice for terminal care, and required resection of all the remaining bowel, leaving the patient with a duodenostomy. High stomal output despite anti-secretory drugs, line sepsis and occlusions, and progressive cholestasis made survival on TPN unlikely and transplantation was considered. The patient's mother donated a 1.8m length of distal ileum on a pedicle of distal superior mesenteric artery and vein. These vessels of supply were anastomosed to the recipient aorta and inferior vena cava. The recipient survived 18 months before dying of pneumonia.

The same team from Leeds collaborated with Japanese surgeons in 1996, the two teams together performing the first Japanese case, in Kyoto. The recipient, a 1 year old child with short gut syndrome received a 1 m length of distal ileum from his mother.

Following these early successes, there have been sporadic cases of living related intestinal transplantation performed, mostly in the US, and by the end of 1996 around 10 cases had been performed. Two of these have employed HLA-identical twin donors—one in California and one in Cambridge. This is reminiscent of the earliest long term survivors of renal transplantation. In the Californian case, a segment which included the ileocaecal valve and right colon was transplanted. The recipient suffered a 'sepsis like syndrome' postoperatively, which would probably have been labelled as rejection-induced bacterial translocation if they had been an allogeneic combination. In this case, it probably reflected a bacterial translocation...
due to a loss of mucosal integrity due to either ischaemia or preservation/reperfusion damage.

The size of the problem

If one extrapolates the findings of a pilot study in North East Thames, UK\(^5\), to a national level, approximately 1–2 patients per million population commence long term TPN each year. Of these, probably more than half would be unsuitable for transplantation on the basis of associated comorbidity or old age, leaving approximately 25–50 potential candidates for intestinal transplantation per year.

In the UK, the use of live donors for solid organ transplantation is an underused resource. Currently, live donors account for just over 10% of kidney transplants in the UK; in 1996, 158 live related transplants were performed, compared with 1519 grafts from cadaveric sources\(^6\). With a predicted annual activity of just 25–50 bowel transplants, one might be tempted to dismiss this potential source of donors. In the US, however, kidney donation from living relatives accounts for around 30% of activity and, in parts of Scandinavia, up to half of the kidneys transplanted are from live donors. Broadly, the medical selection criteria for the donors would be similar and with an enthusiastic approach, a significant proportion of live donors could be used for intestinal donation.

Pre-operative evaluation

Recipient

In assessing the potential recipient of a live-related bowel graft, a number of points must be addressed. Firstly, the need for transplantation—have all attempts to re-establish enteral feeding or of making long term TPN an option been exhausted? Secondly, will a graft consisting of intestine only suffice. If there is cholestatic liver disease with irreversible parenchymal changes, or portal vein thrombosis, then the patient requires a composite liver/bowel graft which requires a cadaveric donor. Thirdly, the state and extent of the remaining intestine, and the patency of the great veins which will probably have been used extensively for central lines in the past must be determined.
Living related intestinal transplantation

Donor

It is essential to confirm the psychological suitability of the donor and to ensure that there has been no coercion employed in the offer to donate. It must be confirmed that there are no immunological contra-indications to performing the transplant, i.e. confirming blood group compatibility with a negative white cell crossmatch. Both parties need to be tissue typed. In addition to confirming the potential donor’s general fitness for a small bowel resection, it is necessary to confirm that their bowel is normal with a duodenal or jejunal biopsy and small bowel enema examination which will also be a guide to the length of the small bowel which varies considerably between individuals. The final and most invasive investigation is an angiogram of the superior mesenteric artery, to define a vascular pedicle on which the graft can be raised.

Technical considerations

As mentioned previously, preoperative mesenteric angiography is performed in the donor, in order to define a vascular pedicle for the graft, which can be used to revascularise the transplant in the recipient. The graft will be a loop of distal ileum through necessity, since it is the terminal portion of the superior mesenteric artery which will be used as the pedicle to the graft, and this supplies the distal ileum. There is commonly a segment of the superior mesenteric artery which is free of branches just beyond the origin of the right colic artery which is convenient to use as the pedicle for the graft (Fig. 1). There are certain physiological advantages in using ileum, which bears receptors for vitamin B$_{12}$ and bile salts and, unlike the jejunum, has tight junctions to allow the absorption of water and solutes against a concentration gradient. A disadvantage is that the ileum has less capacity for adaptation than jejunum. It is possible to include or exclude the ileocaecal valve and caecum and right hemicolon from the graft — both techniques have been successfully employed, although there is a recognised risk of diarrhoea in the donor, and removal of the entire distal ileum may lead to impaired vitamin B$_{12}$ absorption. In our unit, we consider that preserving the terminal ileum and ileocaecal valve in the donor is desirable.

Retrieval technique

At operation, lifting up the small bowel with a powerful light shining through the mesentary will enable the blood vessels to be clearly seen,
and aid in the identification of the distal superior mesenteric pedicle where it is to be divided. This pedicle is isolated, clearing around 2 cm of vessel. The entire small bowel is carefully measured and a decision made as to how much bowel is to be transplanted and how much is to be retained. In our first case, we measured the bowel at 420 cm: 180 cm were transplanted leaving 240 cm in the donor. It is generally accepted that 100 cm is the minimum length of bowel required to allow enteral nutrition independent of TPN in an adult if there is a terminal stoma. If there is an intact colon, which allows some water and solute reabsorption but also adapts to develop some small bowel type absorptive functions, 60 cm can be adequate, and if there is a competent ileocaecal valve in addition to an intact colon, this maintains relative sterility in the small bowel, absorption is more effective and as little as 30 cm of small bowel can allow independent enteral nutrition.7

The desired length of bowel is measured; we favour retaining the ileocaecal valve and distal 25 cm of small bowel and start measuring from this point, proximally to define the loop to be transplanted. The mesentary is divided from the pedicle to the bowel wall at the chosen points of transection (Fig. 2). There is plenty of flexibility in determining the segment to be removed even after the pedicle is mobilised because of
Living related intestinal transplantation

• At Fig. 2 Fully dissected donor graft

The bowel is divided using a GIA® instrument (Autosuture, USA) which delivers two rows of staples and cuts the bowel between them. A seromuscular suture is used to mark the proximal end of the graft, since it is very difficult to tell once the graft is removed.

The donor is given a bolus of 5000 U of intravenous heparin and the vascular pedicle clamped and divided. Once removed, the graft is placed in a bowl of cold saline and the artery flushed with a cold kidney preservation solution at 4°C to remove the blood. The graft will blanch and stop peristalsing. Perfusion is stopped after 200–300 ml of fluid have been run through the graft, once the venous effluent is running clear and free of blood. It should be unnecessary to then perfuse the graft with a longer term preservation solution, such as UW solution, since the donor and recipient procedures should be coordinated such that the graft is only removed when the recipient team are ready to start implantation. This manoeuvre may be necessary, however, if there are logistic problems in performing both operations at once, and donor and
recipient procedures are to be performed in series rather than in parallel. Following removal of the graft, continuity is restored in the donor by a standard end-to-end anastomosis of the small bowel. Postoperative hospitalisation should be less than 1 week during which time the donor should receive all those prophylactic measures normally employed to reduce the risk of deep vein thrombosis, chest infection and wound infection.

**Implantation technique**

Whilst it would seem physiologically better to ensure that the venous outflow of the graft was into the portal system, in order to allow the liver to exert a first pass effect on the draining blood, this is generally not feasible for the graft from a live related source because the blood vessels are so short. Provided that liver function is normal, however, this does not seem to create any problems that might be predicted, such as encephalopathy. It may occasionally be possible to anastomose these vessels onto the stumps of the native superior mesenteric vessels or even to the splenic vessels but, generally, they will be conveniently anastomosed to the front of the recipient infrarenal aorta and inferior vena cava.

Exposure of these vessels may be difficult due to postoperative adhesions and loss of the normal tissue planes as a consequence of previous surgery. Also, extensive previous resection may lead to contraction or obliteration of the peritoneal cavity making implantation of the graft technically challenging.

The artery supplying the graft is 4–5 mm in diameter. This is anastomosed using interrupted 7/0 non-absorbable sutures to a matching sized arteriotomy in the aorta which can be conveniently fashioned using an aortic punch having applied a side-biting aortic clamp. The vein is sutured to a venotomy in the front of the inferior vena cava. To encourage colonisation and adaptive changes, intestinal continuity should be restored by anastomosis of the proximal end of the graft to the recipients own stomach, duodenum, or proximal jejunum if any remains. The distal end is brought out as a stoma since there is a need for frequent mucosal biopsies when monitoring for rejection, and also a need to monitor the bacteria in the effluent since, during rejection, the results of these cultures will determine the appropriate antibiotics to be used to treat the ensuing sepsis. If the recipient has any native distal gut this can be anastomosed to the side of the distal graft. The stoma should only be closed once the need for monitoring has passed and since late rejection is a feature of the transplanted intestine; this should not be
before 6 months. It is still possible to biopsy the graft after the stoma has been closed, but requires formal upper or lower GI endoscopy.

Advantages of live donation

Apart from satisfying a desire to help a family member there are a number of medical advantages in using a live donor for intestinal grafting. One of the paradoxes of intestinal transplantation is that, unlike the kidney, liver and heart, the intestine is not a sterile organ and if it suffers a rejection attack, loss of mucosal integrity leads to bacterial translocation and sepsis, rather than organ failure per se. The paradox is that, during a rejection episode, when the patient is most vulnerable to overwhelming sepsis, there is a need to increase rather than reduce immunosuppression. Long term, the exposure to the powerful immunosuppression required to protect this highly immunogenic graft does substantially increase the risks of both opportunistic infections such as cytomegalovirus and Pneumocystis carinii, and also some types of tumours.

Use of a parent to donate to an offspring or vice versa will generally ensure one shared haplotype or 3 out of 6 shared HLA antigens (two Class I and one Class II). Or there may be a fortuitous matched antigen due to a shared antigen between the parents.

Using a sibling will produce a haplotype matched graft in 50% of cases; 25% will be unmatched and 25% will be HLA identical. In addition to these classical Class I and Class II HLA tissue typing antigens, there will also be other shared antigens on the vascular endothelium which will improve tissue matching and possibly reduce the risk or at least the severity of the rejection. Certainly, in renal transplantation, haplotype matched live related grafts fare immunologically better than 3/6 antigen matched cadaveric grafts from an unrelated source.

Apart from less graft loss from rejection, the ability to use less immunosuppression should reduce the incidence of both opportunistic infections, and those tumours which are associated with excessive immunosuppression. The most serious of these is the lymphoma, which has been a major cause of morbidity and mortality in recipients of cadaveric grafts. The majority of these lymphomas are due to proliferation of B cell clones in response to Epstein–Barr virus, the normal T cell constraint being impaired by immunosuppression, particularly with biological anti-T cell agents.

The live-related transplant can be performed as an elective procedure, when both recipient and donor are in the best possible condition, and
after a complete evaluation of the donor rather than the cadaveric transplant which by necessity has to be performed as and when a suitable graft becomes available.

By coordinating the donor and recipient operations, and using adjacent operating theatres and parallel medical teams, ischaemia times can be minimised, thus reducing the risk of ischaemic damage to the graft. In addition, fairly strict criteria are applied to potential cadaveric bowel donors and, if demand for intestinal grafting increases, cadaveric donors may be in short supply.

**Disadvantages of live donation**

The most obvious disadvantage is that, unlike using a cadaveric graft, the use of a live donor submits the donor to a risk. Firstly, there is the risk of the operative procedure, both in terms of general complications, such as deep vein thrombosis, pulmonary embolus, chest infection, wound infection, *etc*, and also the specific risks related to the surgery, such as anastomotic leakage or stenosis, or peritoneal adhesion formation.

In addition, there is a risk of problems as a consequence of undergoing a major small bowel resection. The shortened length of intestine and reduction in the absorptive area could lead to a degree of intestinal hurry and malabsorption. Loss of the distal ileum could selectively impair the ability to absorb vitamin $B_{12}$/intrinsic factor complex leading to $B_{12}$ deficiency. Loss of the ability to reabsorb bile salts (these receptors are also concentrated in the terminal ileum) can lead to diarrhoea due to the irritant properties of bile salts in the colon.

The use of identical twin donors raises another concern which is not purely theoretical. Massive intestinal infarction may result as a consequence of a prothrombotic state such as deficiency of protein C, protein S or anti-thrombin III. If this is an inherited disorder, then the identical twin will share the abnormality and a laparotomy and bowel resection for donation could precipitate a mesenteric thrombosis in the donor. Certain prothrombotic states have yet to be defined and this exact case scenario occurred in the Cambridge case, although correct identification of the prothrombotic state and aggressive anticoagulation prevented any infarction in the donor in this case.

The use of a live donor will inevitably provide a graft which is considerably shorter than a cadaveric graft, which would be expected to have less functional reserve than a whole organ.

Finally, it should be noted, that the use of live donors potentially opens the doors for the undesirable sale of organs. This practice is illegal in the
Living related intestinal transplantation

UK, but common in the third world, in the field of renal transplantation. It is essential that the same strict rules are applied to live donation of intestine as are to kidney donation in UK, with central registration of all cases and tissue type confirmation of any claimed relationship. The physicians involved with the case must be absolutely satisfied that no coercion is being brought to bear on the potential donor. On occasions, live unrelated kidney transplants are undertaken in the UK. Such cases are strictly monitored by the UKTSSA (United Kingdom Transplant Support Service Authority) to ensure that there is no financial motive behind the donation. Comparable administration must be employed if any enthusiasm develops for live unrelated intestinal transplantation. To date no such case has been reported.

Economic considerations

As with any new modality, the question of cost inevitably arises. Whilst intestinal transplantation is generally considered as an option only for those patients who are suffering complications from TPN, such as cholestatic liver disease and problems with access sites (thromboses and infections), maintenance on TPN is the only useful yardstick with which to compare the costs of a transplant. One might predict that, in the future, with advances in technique and immunosuppression, transplantation (live donor or cadaveric) might become an alternative to TPN rather than a last resort salvage for the dying patient.

Currently, TPN administered at home costs £40–60,000 per year if administered through a commercial company, but perhaps half this amount if organised through a hospital pharmacy. If the patient requires hospitalisation, the costs are around £85,000 per year.

The assessment costs of the recipient and the donor amount to around £5000. The hospitalisation and operation on the donor would cost around £3500 and the transplant procedure and aftercare for the first year including hospitalisation and all drug costs amounts to around £65,000. Assuming a favourable outcome, the annual maintenance costs thereafter are largely due to the immunosuppressants and amount to around £12,000.

These figures, therefore, compare favourably with TPN costs and cost alone should not be a deterrent to considering intestinal transplantation in the TPN dependent patient.
Conclusions

The technical feasibility of live related intestinal transplantation is proven, although there is, of course, the inherent risk of major surgery to the donor, and the donor procedure can never be considered free of risk. There are logistic and immunological advantages in considering live donation over cadaveric donation. The cost of living related intestinal transplantation is comparable to that of maintaining a patient on TPN in the first year, and less expensive in subsequent years. The durability of the graft and thus the long term results, currently remains unknown but the early results should encourage cautious optimism towards the procedure.

References

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