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Brief Communication

Intestinal Transplantation for Chronic Intestinal Pseudo-Obstruction in Adult Patients

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Intestinal transplantation (ITx) has become a life-saving procedure for patients with irreversible intestinal failure who can no longer be maintained on parenteral nutrition (PN). This report presents the results of our experience on ITx in patients suffering from chronic intestinal pseudo-obstruction (CIPO). Between December 30, 2000 and May 30, 2003 six adult patients affected by CIPO underwent primary ITx at our Center. Pre-transplant evaluation, indication for ITx and surgical technique are reported. On December 30 2003, the mean follow-up was 25.0 months. No peri-operative deaths occurred in the study population and five out of six patients are alive, with 1-year patient and graft survival of 83.3% and 66.6%. Although our series is limited by the number of patients, our experience suggests that ITx transplantation should be considered in adult patients suffering from CIPO and PN life-threatening complication.

Key words: Chronic intestinal pseudo-obstruction, immunosuppression, intestinal transplantation, rejection, total parenteral nutrition

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Introduction

Chronic intestinal pseudo-obstruction (CIPO) encompasses a wide array of conditions characterized by a severe impairment of gut propulsive motility with signs and symptoms of intestinal obstruction without evidence of organic causes occluding the intestinal lumen (1,2). Depending on the impairment affecting gut control systems (mainly smooth muscle or nerves supplying the digestive system), CIPO can be defined as myopathic, neuropathic or neuro-myopathic. Also, the syndrome can be either secondary, as it results from several potentially treatable diseases, or idiopathic if no underlying conditions can be identified. The onset of CIPO can occur at any age with a variable degree of symptoms including abdominal pain, distension, nausea, diarrhea/constipation and with laboratory abnormalities which may reflect the degree of malabsorption and malnutrition. The diagnosis of CIPO is mainly clinical and aimed at excluding mechanical subocclusion by endoscopic and/or radiological investigations. Although not crucial for diagnosis, small bowel manometry is an important test because it contributes to the differential diagnosis between functional and mechanical obstruction, it helps to establish the extent of dysmotility throughout the gastrointestinal tract and, finally, it suggests myopathic or neuropathic forms of CIPO (3). Management of CIPO is largely conservative and focused on maintenance of optimal nutrition by enteral or parenteral routes (4). Despite an adequate length of bowel, patients with CIPO are often intolerant to enteral feeding and they end up being dependent on parenteral nutrition (PN). Although beneficial in the short-term management of CIPO patients, PN is aggravated by a considerable mortality rate primarily related to the life-threatening catheter-related complications (5). Adult patients affected by CIPO in whom continuation of PN is not possible may benefit from intestinal transplantation (ITx) (6). In this report we described our results with ITx in adult patients with CIPO.

Patients and Methods

On December 30th, 2000, an ITx program was initiated at the Liver and Multivisceral Transplant Center of University of Modena (Italy). Between that date and May 30th 2003, 19 adult patients underwent primary ITx. An established diagnosis of idiopathic CIPO was achieved in six patients, which constituted the base of this report. Transplantation evaluation included barium studies of the gastrointestinal tract to establish length and anatomy of the intestine.

Small bowel manometry was performed whenever possible to evaluate the extension of the affected segments of the alimentary tract. Specifically, small bowel manometry was performed by a stationary perfused technique as previously described (7); motility was recorded for at least 6 h during fasting and 1 h post-prandially; tracings were visually analyzed to detect abnormal motor patterns as previously reported (8). Gastric emptying studies were not performed due to the inability of all patients to eat the standard test meal.

Table 1: Main demographic, nutritional, manometric and surgical features of investigated patients

Pt	Age	Sex	Caloric intake before ITx	Manometric abnormalities	Graft type	Status before ITx	ICU stay	Hospital stay	PN discontinuation (days) after ITx
1	37	M	100% PN	NP	ISB	ICU	4	37	20
2	21	F	100% PN	1/3 ABN AF (prop) 1 burst	ISB	Home	3	28	12
3	28	F	80% PN/20% enteral	1/2 ABN AF (prop)	MV w.o.liver	Hospital	5	45	24
4	37	F	75% PN/25% enteral	NP	ISB	Home	8	29	39
5	30	F	100% PN	1/2 ABN AF (prop) 2 bursts	ISB	Hospital	4	48	31
6	31	M	70% PN/20% enteral	2/2 ABN AF (conf)t	ISB	Home	3	40	no discontinued

NP: not performed; ABN AF: abnormal activity front; PROP: propagation; CONF: configuration.

Indication for ITx was irreversible intestinal failure associated with one or more life-threatening complications that included a mild to moderate liver injury disease from cholestatic liver cirrhosis with fibrosis on liver biopsy and portal hypertension with hepatosplenomegaly, ascites and esophageal varices which are signs of irreversible liver disease. Frequent central venous catheter infections due to multi-drug-resistant organisms with a high risk of morbidity such as metastatic abscess, infective miocarditis or multi-organ failure which can eventually lead to loss of the central venous access site. Major fluid/electrolyte imbalances (associated with proximal gastrointestinal stomas or fistula), extreme bowel dilatation with bacterial overgrowth and intractable abdominal pain were clinical features present in most of the patients. Three different immunosuppression protocols were implemented and consisted of daclizumab (Zenapax®) induction, tacrolimus (target tacrolimus trough blood levels were between 15 and 20 ng/mL) and steroids (protocol no. 1), alemtuzumab (Campath®) induction, low-dose tacrolimus (target tacrolimus trough blood levels were between 10 and 15 ng/mL) with no maintenance steroids (protocol no. 2), anti-thymocite globuline (Thymoglobuline®) induction, tacrolimus (target tacrolimus trough blood levels were between 15 and 20 ng/mL) and steroids (protocol no. 3). The nutritional management consisted of enteral feeding with dextrose 5% which was started immediately after surgery through a jejunostomy while elemental diet was initiated as soon as the ileostomy was functional and was maintained during rejection episodes. All patients received prophylactic antibacterial and antifungal infection treatment and cytomegalovirus prophylaxis with 5 mg/kg gancyclovir twice a day and with cytomegalovirus-specific immunoglobulins for 1 month after surgery.

Data sources included: case records, outpatients charts, computerized database. No patients were lost to follow-up and the study was concluded on December 30th, 2003. The aim of the study was to determine the results of intestinal transplantation in adult patients affected by CIPO, with special emphasis on surgical techniques.

Statistical methods

Survival was calculated using the method of Kaplan–Meier. Continuous variables were reported as mean ± standard deviation.

Results

All patients were adults with a mean age of 30.6 years (SD ± 6.7). Four recipients were female, 2 were male. Three patients met their full caloric requirements from PN at the time of transplant, in the remaining three enteral feeding was tolerated up to 20–30% of caloric intake. The mean pre-operative duration of PN before transplant was 9.1 years (SD ± 3.6). Two patients could not maintain a normal nutritional status because they had adverse reactions to the parenteral nutrition solution and needed high doses of analgesics to control abdominal pain. The other four patients had significant infectious complications from PN; all of them had recurrent serious sepsis secondary to central venous catheter infections with concomitant loss of at least one vascular access site. Two out of six had mild fibrosis associated with cholestasis at the liver biopsy; these signs were interpreted as potentially reversible if the PN could be discontinued.

Five patients received isolated small bowel (ISB) while only one received modified multi-visceral (MV) grafts (including stomach, duodenum, pancreas and small bowel), with no liver (9–11). At the time of transplant one patient (16.7%) was in the intensive care unit (ICU), three patients (50.0%) were hospital-bound while the other two (33.3%) were at home. Table 1 summarizes the main demographic, manometric and clinical features of the patients involved in the study. All intestinal/multi-visceral grafts were removed from multi-organ cadaveric donors with identical ABO and random human leukocyte antigen (HLA) match. Lymphocytotoxic cross-match was negative in all patients. The mean donor age was 30.6 years (SD ± 11.1). All donors were cytomegalovirus (CMV) negative. Details of the surgical technique for different types of ISB/MV allografts have been described elsewhere (12,13).

In the five patients who were submitted to isolated small bowel transplantation, gastrointestinal continuity was achieved in two cases by performing a side-to-side duodeno-jejunostomy; while in the remaining three cases a modification of the procedure with a hemigastrectomy was performed. For MV transplantation, reconstruction of the proximal gastrointestinal tract was achieved by performing an anastomosis between the native esophagus and the anterior wall of the stomach. In all cases, distal continuity was established with an end-to-side anastomosis between the graft and the distal colon or rectum with a temporary ileostomy for anastomotic protection and mucosa monitoring (14). The mean cold ischemia time was 5.8 h (SD ± 1.3) and the mean operative time was 10.4 h (SD ± 1.15). The mean ICU stay was 4.5 d (SD ± 2.1). The median hospital stay was 38.3 d (SD ± 13.4). On December 30th 2003, the mean follow-up was 25.0 months (SD ± 11.2 months). All patients in this series were followed for a minimum period of 14 months. No peri-operative deaths occurred in the study population. After discharge, patients experienced

Table 2: Type of immunosuppressive protocol, type of surgery and outcome

Pt	Graft type	Immunosuppressive protocol	Gastrointestinal continuity	Nausea	Vomiting	Note	Outcome
1	ISB	daclizumab induction	Gastro-jejunostomy	Mild	NO	Oral feeding from 7 POD	Alive and well
2	ISB	daclizumab induction	Gastro-jejunostomy	Mild	NO	Oral feeding from 10 POD	Alive at home (100% PN), waiting for Re-ITx
3	MV wo liver	daclizumab induction	Esophago-gastrostomy	YES	YES	Daily stomach venting	Expired
4	ISB	daclizumab induction	Gastro-jejunostomy	NO	NO	Oral feeding from 8 POD	Alive and well
5	ISB	alemtuzumab induction	Duodeno-jejunostomy	Severe	YES	Oral feeding from 28 POD	Alive and well
6	ISB	antithymocite globuline	Duodeno-jejunostomy	Severe	YES	Oral feeding from 17 POD	Alive at home (100% induction PN), waiting for Re-ITx

readmission for a mean of 3.4 times/year (SD $\pm$ 1.8) with an average stay of 9.5 d (SD $\pm$ 7.4). The most common indication for readmission was dehydration as a consequence of high stomal output and recurrent diarrhea. This complication disappeared with the closure of the ileostomy. Infections and acute cellular rejection (ACR) episodes were other important indications for readmission. Graft vs. host disease was not seen in this series. Five out of six patients experienced at least one episode of biopsy-proven ACR (83.3%), among them the incidence of rejection episodes per graft was 3.4 (SD $\pm$ 2.2). No ACR episodes were seen in the patients treated with the alemtuzumab induction protocol. Rejections were treated with steroid boluses and tapering, and all but one of them evolved to complete resolution in a maximum of 5 days. In one patient (no. 6) a severe ACR required a course of OKT3 treatment with no resolution; the patient ultimately underwent graft removal and the patient is on the waiting list for re-transplantation (Thymoglobuline induction protocol). Two years after ITx, patient no. 2 developed a progressive intolerance of enteral feeding, with nausea and vomiting associated with abdominal distension. Radiologic contrast studies showed a severe hypomotility of the transplant bowel. To explain this clinical picture, a hypothesis of chronic rejection was formulated. The patient needs total PN support and she is on the waiting list for re-transplantation.

The only patient who underwent MV transplantation did so because of severe duodenum dilatation responsible for recurrent sepsis due to duodenal bacterial overgrowth. The post-operative course of the MV transplantation recipient was characterized by delayed gastric emptying with nausea associated with vomiting unless daily venting of the stomach was performed. This patient ultimately died after more than 10 months from unremitting hemolytic–uremic syndrome with a functioning graft off PN on full enteral feeding by mouth. All five ISB recipients are alive with overall 1-year patient and graft survival of 83.3% and 66.6%, respectively.

Of the other five patients who underwent ISB transplantation, the stomach was left intact in two of them because the pre-operative study did not show severe gastric dismotility and both of them had delayed gastric emptying with significant morbidity. In the remaining three patients a hemigastrectomy with a gastro-jejunostomy was performed and all of them had mild signs of nausea without vomiting in the post-transplant period (Table 2).

No patients experienced major bacterial and fungal infectious complications. Four patients experienced CMV positivization due to a reactivation of a latent infection concomitant with rejection treatment. All the episodes resolved in a period of 7–14 d with gancyclovir treatment.

Discussion

Patients afflicted by intestinal failure and PN-related life-threatening complications have a poor chance of long-term survival. In these patients, ITx should be considered in order to improve prognosis. In fact, since the introduction of tacrolimus, clinical ITx has shown a slow but continuous improvement of patient and graft survival (15). There is a concern that patients affected by CIPO may require a multivisceral transplant with removal of the native stomach. As reported by Sigurdsson et al. (6) all patients who received an allograft stomach had delayed gastric emptying and documented gastric bezoars showing that the multi-visceral graft did not eliminate the underlying problem of dysmotyliity and all multi-visceral recipients continued to have delayed gastric emptying (6). The only patient who received an allograft stomach in our series suffered from the same problem. Iyer et al. from Omaha (16) showed reduced hospital and intensive care unit stays for the isolated intestinal graft recipients compared with the liver/small bowel recipients and a more rapid return to enteral feedings (17). According to the Intestinal Transplant Registry, grafting with isolated small bowel allografts provided better overall patient survival rate and graft function at all follow-up times (18). Howard et al. (19) showed a 2-year mortality rate of 30% in patients with CIPO or ischemic bowel, of 20% in those with congenital bowel disease and of 10% in patients with Crohn's disease with most deaths of CIPO patients

being related to the disease. However, the PN complication rate in CIPO patients was about twice that of other PN patients with benign disease (19). This may be due to the patients' impaired ability to manage line sterility when receiving high dose of opiates or sedatives to control pain which contribute to the lower quality of life experienced by patients with CIPO (20).

Our experience showed that multidisciplinary pre-transplant management is mandatory and surgery must be tailored to each individual because the disease can affect different portions of the digestive system. Patients who underwent ISB transplantation associated with partial gastrectomy had a more favourable post-operative course with mild nausea and no vomiting.

Although our series is limited by the small number of patients, our experience suggests that ITx transplantation should be considered in adult patients suffering from CIPO and PN life-threatening complications, in particular ISB transplantation associated with partial gastrectomy can allow good results in this difficult group of patients with an improved outcome.

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