Adult Small Intestinal and Multivisceral Transplantation: Lessons Through the “Retrospecto-scope” at a Single UK Centre From 1991 to 2013


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ABSTRACT

The first intestinal transplantation in the United Kingdom was performed in Cambridge in 1991. Thirty-eight intestinal transplantations have since been performed in 35 patients. All deaths in the first postoperative month related to hemorrhage, in 2 cases to severe portal hypertension (SPH) and poor venous access in 2. We have modified our practice to reduce the bleeding risk with SPH. Loss of venous access can be avoided by timely referral. Rejection was implicated in 3/14 deaths all dying of sepsis. Cytomegalovirus disease resulted in 2 deaths; we try to avoid CMV-positive donors giving to CMV-negative recipients. Three deaths were related to psychiatric illness, which led to loss of graft in 2 others. Three patients were retransplanted (2 rejections and 1 infarction) and all remain alive. Most patients (10/13) experienced a fall in body weight in the first postoperative year after SB/MV transplantation. Body weight fell by as much as 25%. As transplantation resulted in a net gain in small bowel in most cases, the postoperative loss of native body weight may be underestimated. Interestingly this was not associated with a significant fall in midarm circumference or handgrip strength. Long-term nutrition can be maintained with oral intake in the majority of patients post-SBT. There is improvement in handgrip strength post-transplant. Transplantation does not significantly alter weight, albumin, or other common anthropometric markers. Despite these problems, our 5-year survival results remain relatively good at 73% in the cohort from 1991, 79% from 2003, and 80% from 2008. We consider that deployment of strategies learned from our experiences has improved outcomes.

INTESTINAL TRANSPLANTATION either as an isolated graft or in conjunction with other organs as a multivisceral graft is now considered as a standard treatment option for patients with intestinal failure [1,2]. Nevertheless, intestinal transplantation remains an uncommon procedure with fewer than 100 transplants per annum currently being performed worldwide. It is normally reserved for those who cannot safely continue on parenteral nutrition (PN) [3], and the decision to transplant is largely influenced by the relative survival risks of continuing PN or undertaking the complex process of transplantation [4]. Occasionally patients are considered as candidates as a consequence of very poor quality of life on PN. The risks associated with this procedure are considerable and difficult to accurately quantify. Progress has been facilitated by the use of an international registry [1], which allows learning from the collective worldwide experience. This is an invaluable resource and has influenced the management of these patients. More detailed experiences of individual centers are also important and can inform practice [5–8]. Often problems encountered are peculiar to individual centers and need to be identified by audit processes, analyzed, and corrected. However, other centers can also learn from these lessons. We have reviewed our patients’ management and focused on the causes of mortality and

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serious morbidity as well as nutritional status. From this review, we have made informed changes in practice.

METHODS
A review of all intestinal and multivisceral transplants undertaken at Addenbrooke’s Hospital, Cambridge University, United Kingdom, National Health Service trust since the program was undertaken in 1991. Data were collected both retrospectively from case notes and computer data bases and prospectively from data collection sheets and weekly event monitors of all patients. Patients were assessed in detail pretransplantation as a routine and all comorbidities were fully characterized. Nutritional status was evaluated with anthropometric measurements. The causes of death were fully characterized and investigated to identify the factors involved, particularly those that might be avoided in the future by a change in practice.

RESULTS
Thirty-eight small bowel transplants have been undertaken in 35 patients. Survival rates are shown as Kaplan-Meier plots for overall cohort and those undertaken in the modern era since 2006 (Figs 1 and 2). Nineteen patients received a multivisceral, 12 an isolated intestine, and 7 a modified multivisceral graft (Fig 3).

Primary diseases were Crohn’s (9), port-mesenteric vein thrombosis (6), related to alcohol cirrhosis (2) antithrombin 3 deficiency (1), cystic fibrosis (1), trauma (1), and Jak 2 mutation (1), superior mesenteric artery thrombosis (7), desmoid tumor (4), dysmotility (4), gastrochisis (1), surgical complication (2), radiation enteritis (1), volvulus (1) (Fig 4).

Death occurred in the first week in 4 patients, 3 at the time of surgery. One patient died from uncontrolled hemorrhage at the time of attempted insertion of a mediastinal line, and 2 patients experienced severe bleeding during the initial surgical dissection from collateral veins consequent upon occlusion of the portomesenteric veins and severe portal hypertension. This was associated with the development of severe acidosis and hyperkalemia. Another patient developed coagulopathy related to massive blood transfusion during surgery.

One patient died in the first month from bleeding and lost venous access making blood replacement and renal support impossible. In addition, 4 patients died in the first postoperative year, 1 developed rejection and subsequent overwhelming sepsis, and another had graft ischemia secondary to severe aortic atherosclerosis, which was apparent preoperatively. Another patient developed disseminated leiomyosarcoma from a tumor arising in the gastric wall of the explanted organ block, which had not been recognized preoperatively. Overwhelming cytomegalovirus (CMV) disease resulting in multiorgan failure accounted for a further death in the first postoperative year.

There were 6 more deaths after the first year. One patient developed sepsis related to biliary stasis and cholangitis, rejection, and sepsis from gut translocation leading to multiorgan failure occurred in 3 more. One patient developed pneumonia and died after a lung biopsy, and another patient died from head injury sustained during a fall in his home 5 years post-transplant.

Change in Practice as a Result of Factors Associated With Mortality
All deaths in the first postoperative month related to severe hemorrhage, in 2 cases due to severe portal hypertension (SPH) and acidosis, and poor venous access in another 2. We have modified our practice to reduce the bleeding risk associated with SPH. Patients are placed on pre-emptive venovenous bypass, which allows a degree of decompression of the inferior vena cava and hence collateral portosystemic shunts. This also allows pre-emptive hemofiltration to avoid severe acidosis and hyperkalemia, which can be particular
problems at reperfusion of the graft. Loss of venous access can be avoided by timely referral. We have also started a practice of vascular reconstruction using donor vessels to replace obstructed major veins allowing intravenous access during the peri- and postoperative period. To achieve this we have undertaken an superior vena cava to subclavian graft using donor aorta and internal iliac to inferior vena cava graft using donor aorta. These grafts have remained patent and 1 was subsequently used as venous drainage for a renal graft. Rejection was implicated in 3/14 deaths, all of subsequent sepsis. CMV disease resulted in 2 deaths; we try to avoid CMV-positive to CMV-negative transplants. Three deaths were in part related to mental illness, which led to loss of graft in 2 others. In most of these cases, patients became noncompliant with antirejection therapy. One patient also refused lifesaving dialysis. We have focused on this area also and improved our management of patient expectation as well as enhanced our psychosocial support. Three patients were retransplanted (2 rejections and 1 infarction) and remain alive. Attempts are made to optimize preoperative nutritional status and the benefits of this are assessed in the context of the risk associated with delaying the transplant procedure.

Nutrition

Nutritional status was assessed before and after small bowel transplantation over the period 2006 to 2012. Thirteen (10 male, 3 female) patients had 15 transplants. Five (33.3%) were isolated small bowel transplantation, 9 (60.0%) were multivisceral, and 1 (6.7%) modified multivisceral transplant. Mean age at SBT was 41.6 years (standard deviation [SD] 9.5; range 29 to 60 years).

Nutritional Status in the First Postoperative Year

Preoperative parameters were compared to lowest postoperative values found in the first year (the nadir; Fig 5).

Body weight (BW) fell significantly from a preoperative mean (SD) of 64.6 (14.4) to a postoperative mean of 58.8 (11.96) kg (Fig 6; Wilcoxon signed rank test (WSR) 0.016 (2 tailed). Ten patients experienced a fall in BW: mean (SD) −10.72 (8.3)% and 2 a rise: 14.2 (7.6)% with overall mean change (CI) of −6.8 (−14.3–0.53)%. This resulted in a significant fall in body mass index (BMI) (mean (CI) from 21.5 (19.4–32.6) to 19.7 (17.8–21.6); WSR = 0.033). BMI fell in 10 patients: −11.8 (−17.2 to 6.34)%; and rose in 2: 7.11 (−14.6–28.8)%. Handgrip strength (HGS) did not alter significantly (WSR = 0.85) rising in 6 patients: mean (CI) 24.5 (0.19–48.7)% and falling in 6: −20.15 (−33.3 to −7)% with an overall change of 2.16 (−16–20)% (Fig 7). Midarm circumference (MAC) fell in 8 patients 13.3 (−18 to −8.9)% and rose in 5: 7.3 (−4.7–19.2) with an overall change of −5.4 (−12.9–2.14)%. BW and BMI remained the same in 1 patient and HGS was not available in 1 patient. The maximum individual fall in BW and BMI in the first postoperative year were measured at 25.8% and 25%, respectively.

Most patients (10/13) experienced a fall in body weight in the first postoperative year after small bowel/multi-visceral transplantation. BMI fell by as much as 25%. The transplant procedure resulted in a net gain in small bowel and consequently body weight, which may have resulted in an underestimate of the loss of native body weight during recovery after transplantation. Interestingly this was not associated with a significant fall in MAC or HGS, although there was a trend for HGS to increase and MAC to fall.

Nutritional Status in the Longer Term

Longitudinal anthropometric data were also routinely collected to assess nutritional status and allow timely intervention if appropriate. Seven patients (53.8%) were on PN pretransplant, with 4 (30.1%) on oral nutritional...
supplements. Mean handgrip (age- and gender-adjusted) pretransplant was 67.5% (SD 17.9%). Anthropometric studies were carried out on average 209 (SD 173) days pre-transplant. Mean duration of PN post-transplantation was 26.9 (SD 33.4) days, with median 18 days. Ten patients maintained nutrition orally in the long term, 2 patients required enteral supplementation, and 1 (who had subsequent small bowel infarct and enterectomy) required parenteral support. Mean handgrip strength reduced by 13.8% (SD 19.2) in the initial 3 months post-transplantation, and improved by 6.5% (SD 15.9) within 6 months, 6.6% (SD 15.9) within 12 months, 8.5% (SD 27.4) within 24 months, 15.3% (SD 13) after 24 months. If the 2 deceased patients were excluded, there was significant improvement in handgrip strength on Student $t$ test ($P = .005$). There were 2 patients whose handgrip did not improve in the long term follow-up, with handgrip reduction of 36% and 9% after 6 months post-transplant. The first patient had severe refractory small bowel rejection and multiorgan failure. The other had restrictive eating pattern with gastroparesis, pancreatic insufficiency, and bacterial overgrowth. There was no significant improvement to mid-arm circumference, mid-arm mean circumference, and triceps. There was loss of weight post-transplantation by the end of nutritional follow-up (mean 3.4 kg with SD 7.8 kg).

Change in Practice From Nutritional Point of View

In light of the observations that in the first postoperative year body weight can fall by as much as 25% and that in the longer term it is not increased on average, our approach to patient’s preoperative workup has changed to increase the intensity of nutritional preparation of patients. This can result in delaying the transplant procedure until the nutritional status has adequately improved. Furthermore, these findings allow better informed consent of the patients who should not expect a high chance of overall weight gain but can expect an improvement in muscle function as evidenced by the significant improvement in HGS.

DISCUSSION

Reported survival rates in the literature vary widely between centers [1], and this is likely to reflect the differences in case selection and the types of procedures undertaken at each center [5]. We have found the practice of regular audit and identification of recurring problems in the management of our patients allows modification of protocols and has been associated with excellent rates of survival. Some of our observations have been concordant with reports from others, such as the adverse effects of CMV infection on survival [9]. Since 2006 we have observed 100% 5-year patient survival for those receiving isolated small bowel grafts. For all types of procedures we have seen an improvement in 5-year survival from 73% in the cohort from 1991, 79% from 2003, and 80% from 2008. Deployment of strategies learned from our experiences should improve our survival outcome over the next era.

Long-term nutrition can be maintained with oral intake in the majority of patients post-SBT. There is significant improvement in handgrip strength post-transplant, which remains an important marker of clinical nutritional status. Others have reported similar and more widespread improvements in nutritional status after transplantation [7,10]. However, in our experience, in adults, transplantation does not significantly alter weight, albumin, or other common anthropometric markers. When discussing the option of transplantation with patients this information is important to fully inform them of the likely outcome after transplantation. Often patients are expecting a dramatic improvement in nutritional status, which is not likely to be achieved according to our observations, but an improvement in strength may be expected. Given the observation that there may be a fall in body weight by as much as 25% in the first postoperative year, patients and relatives should be prepared for this possibility and clinicians mindful of the fact that if patients are malnourished preoperatively, this may deteriorate considerably further in the postoperative period.
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