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Surgical complications after intestinal transplantation in infants and children—UK experience

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Abstract Surgical complications have a significant impact on morbidity and mortality following intestinal transplantation (ITx). Birmingham Children's Hospital commenced intestinal transplantation in 1993 and the following surgical strategies evolved: (a) pretransplant abdominal tissue expanders, 1998; (b) combined en-bloc reduced liver and intestinal transplantation (CRLITx), 1998; (c) staged abdominal closure, 2001; (d) preservation of graft duodenal artery, 2005.

Aim: An internal audit was performed to document the surgical complications after ITx and to evaluate strategies in the management and prevention of complications.

Methods: A retrospective analysis of the medical records from January 1993 to June 2007 was conducted to identify surgical complications, evaluate management strategies, and report outcome following ITx.

Results: Forty-six children underwent 49 ITx (9 isolated intestinal, 39 combined liver and intestinal [CLITx], and 1 multivisceral transplant). Twenty three children had CRLITx since 1998, although there were none before 1997. The median donor: recipient weight ratio in CLITx was 2.2:1 (range, 0.67:1-6.70:1). Twenty-six children experienced 29 (59%) surgical complications: portacaval shunt thrombosis (n = 2, none alive); graft duodenal stump leakage (n = 3, 2 alive); spontaneous bowel perforation(n = 6, 2 alive); sub-acute bowel obstruction (n = 6, all alive); abdominal compartment syndrome ([ACS], n = 4, 2 alive); pancreatic leak (n = 3, 2 alive); biliary complications (n = 22, 17 alive) failed staged abdominal closure with wound sepsis requiring skin grafting into the bowel (n = 1, alive), wound dehiscence (n = 1, alive), anastomotic leak (n = 1, alive) and intra-abdominal bleeding (n = 1,alive), primary nonfunction (n = 1, 1 died). Following the complications of ACS in children with primary abdominal closure and graft duodenal stump leaks in 2004, we modified our strategies in 2005 to include staged abdominal closure with recipient to donor weight mismatch, and preservation of the gastroduodenal artery during donor organ procurement in addition to pre transplant abdominal tissue expansion. Fifteen children with recipient and donor weight mismatch subsequently required staged closure of the abdomen and none of them developed ACS. Twelve children had gastroduodenal artery

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preserved and none developed graft duodenal stump leaks. Twenty-four of the 46 (52%) are alive 6 months to 10 years post transplant.
Conclusion: Evolving strategies may avoid or reduce surgical complications commonly seen after intestinal transplantation and thus contribute to an improved outcome.

Intestinal transplantation (ITx) is still in its infancy when compared to kidney, heart, and liver transplantation. However, the results of ITx have continued to improve significantly in recent years. As a result, ITx is no longer an experimental endeavor but is recognized as an established treatment for complicated intestinal failure (defined as irreversible intestinal failure and/or loss of venous access and irreversible parenteral nutrition associated liver disease) with currently a 1- and 3-year survival approaching that of liver transplantation [1].

Immunosuppressive strategies have evolved in the last decade and the prevention, diagnosis and management of graft rejection and post transplant infections are the most common topics discussed in the ITx literature [2,3]. Improved results of ITx are reported from the intestinal transplant registry (http://www.intestinaltransplant.org/) and one of the main factors contributing to the clinical success of ITx besides refinements in immunosuppressive regimens, is the constant progress made in the surgical techniques [1]. Modifications of surgical technique are well reported in the literature and the main types of transplant performed depend on the severity of liver disease: (A) No liver disease or liver disease without significant portal hypertension—liver is not included in the graft and 2 types of transplant are essentially done-Isolated intestinal transplant (IITx) and modified multivisceral transplant (in children with foregut dysmotility). (B) Significant liver disease with portal hypertension—combined liver intestinal transplant (CLITx) and multivisceral transplant (in children with foregut dysmotility since 2005 in our program). However, there has been inadequate focus on the management and prevention of postoperative complications of ITx, especially in young children [4]. The first pediatric intestinal transplant in the United Kingdom took place at Birmingham Children's Hospital (BCH) in 1993. In 1998, to widen the donor pool for smaller recipients and reduce the waiting list mortality, new techniques were introduced, which included combined en-bloc reduced liver and small bowel transplantation (CRLITx) and subsequently, the use of pretransplant abdominal tissue expanders and staged abdominal closure (2001) [5]. In 2005, further strategies of preservation of the gastroduodenal artery at the time of graft procurement and multivisceral transplantation were introduced. The strategies evolved with recognition of newer complications and increasing experience with ITx which have impacted on improved survival following small bowel transplantation.

An internal audit was performed to evaluate the impact of the evolving strategies on surgical complications and report on the outcome.

1. Methods

The liver unit data base and UK transplant data base (consent obtained from parents for entry into both data bases) was analysed retrospectively to identify the children who underwent ITx at BCH between April 1993 and June 2007. Immunosuppressive regimen and cytomegalovirus (CMV) prophylaxis during this time period is as described elsewhere [6]. Medical records and operative notes of these children were reviewed to record the following variables: number of transplants, type of transplant, donor and recipient weight at the time of transplant, type and onset of surgical complications after ITx (Table 1), subsequent management and outcome following surgical complications. The incidence of the surgical complications before and after the implementation of evolving surgical strategies was noted. Because the standard procurement of

Table 1 Definition of surgical complications after intestinal transplantation

Type of complication	Definition
Intestinal perforation	high index of clinical suspicion and confirmed at the time of laparotomy by a transplant surgeon
Abdominal compartment syndrome (ACS)	graft and abdominal organ dysfunction with ischemia, secondary to increased intra abdominal pressure as documented by measuring intra-vesical pressure of greater than 20 mm Hg or clinical impression with marked improvement in condition on decompressive laparotomy
Intestinal obstruction	high index of clinical suspicion, radiological investigations and confirmed on laparotomy by a transplant surgeon
Biliary complications	Intra or extra hepatic biliary dilatation on ultrasound scans or magnetic resonance cholangio-pancreatography
Primary non-function	Severe coagulopathy, progressive lactic acidosis and necrotic bowel within 24 hrs of transplantation

liver-intestine grafts for small children includes the duodenum and pancreas for technical reasons, a "multi-visceral graft" was defined as any graft with inclusion of an additional intraabdominal organ (in addition to the liver, intestine and pancreas (ie, stomach, kidney, etc).

2. Results

Forty-nine ITx were performed in 46 children. These comprised 9 IITx transplants (1 retransplant), 39 combined CLITx and 1 multivisceral graft (included the kidney) . The median weight of children was 11.0 kg (6.2-53 kg) and that of their donors 24 kg (6.4-70 kg), that is, a median donor-recipient ratio of 2.2:1. The median cold ischemic time in the IITx and the CLITx were 6 hours 30 minutes (range, 5 hours 37 minutes to 9 hours 47 minutes) and 7 hours 52 minutes (range, 3 hours 41 minutes to 13 hours 7 minutes), respectively.

2.1. Impact of using CRLITx on number of transplants and death on transplant waiting list

In pre-1998 era, of the 48 children assessed for ITx, 19 children were recommended for ITx, 4 intestinal transplants were performed (2 size-matched liver and small bowel transplant, 2 isolated intestinal transplant), whereas 10 children died on the waiting list. In the post-1998 era, of the 230 children assessed for ITx 98 were recommended for transplant, 45 intestinal transplants were performed (7 IITx transplant and 14 size-matched CLITx, 23 CRLITx; 13 children also had reduction in donor intestinal length), whereas 24 children died on the waiting list. Although the number of intestinal transplants increased during the time-period, the lack of availability of small sized donors in UK resulted in increased deaths on transplant waiting list in children under 10 kg [7].

Twenty-six of the 46 children experienced 29 surgical complications (59%). The rest of the 20 children did not have any surgical complications. The major complications experienced apart from those described below are portacaval shunt thrombosis (n = 2, none alive); biliary complications (n = 22, 17 alive) failed staged abdominal closure with wound sepsis requiring skin grafting into the bowel (n = 1, alive), wound dehiscence (n = 1, alive), anastomotic leak (n = 1, alive), and intra-abdominal bleeding (n = 1, alive), primary nonfunction (n = 1, 1 died).

Three (1 IITx and 2 CLITx) of the 46 children (6%) needed retransplantation as a consequence of chronic rejection in the graft, but none of them experienced any surgical complications in the retransplanted graft.

2.2. Intestinal perforation (n = 9, 4 alive)

Around 33% (n = 9/29) of the surgical complications were intestinal perforations (Table 2). All the intestinal perforations occurred in children receiving CLITx. Of the 9 perforations, 3 were at the site of the donor duodenal stump closure, which had been both stapled and oversewn with sutures, 2 in the recipient duodenum, and 4 spontaneous perforations in the transplanted jejunum. No obvious cause for the perforations were identified at laparotomy. Five children with intestinal perforations died; 2 died as a result of the perforation, but the cause of death in the other 3 was multi-factorial.

Of the 3 children with a perforation in the donor duodenal stump, 2 had a whole CLITx, and 1 had a CRLITx. In the first patient who developed leak in donor duodenal stump, the site could not be identified at initial explorative laparotomy. Multiple radiological investigations performed could not identify the exact site of perforation. Seven weeks later, a relaparotomy was performed for a life-threatening gastrointestinal hemorrhage which finally identified the site of perforation in the stump of donor duodenum. The child died 2 days later from sepsis and multiorgan failure. In the next 2 children, with a high index of clinical suspicion, early operative action was taken. In these 2, the site of duodenal stump perforation was identified at laparotomy, a t-tube was inserted at the perforation site and the perforation was treated conservatively. One of these children had the t-tube removed by laparotomy 6 weeks later, and 1 had it removed in the ward 12 weeks after the initial laparotomy. Both these children had no further problem from the duodenal stump leak.

One patient (CRLITx) had a recipient duodenal perforation 2 cm proximal to the duodenojejunal anastomosis site (Table 1). This patient was treated by laparotomy and insertion of a t-tube, which was removed 6 weeks later in the ward. The patient did not have any further problem from this perforation. The other child (CRLITx) had a portacaval thrombosis and intramural hematoma at the time of transplant. This may have contributed to the weakening of the duodenal wall leading to perforation in the posttransplant period.

Four children had spontaneous small bowel perforations (SBP) (Table 2). One patient (whole graft) had a jejunal and gastric perforation. The gastric perforation was repaired in layers of sutures and a t-tube was inserted in the jejunal perforation. This patient died 5 days later from, pulmonary hemorrhage and overwhelming sepsis. A second patient (CLITx) had laparotomy for a clinical suspicion of perforation. At laparotomy, a large collection was evident but the site of intestinal perforation could not be identified. This patient died from respiratory failure 12 days later. Two other children (1 CLITx, 1 CRLITx) had spontaneous jejunal perforations. One, treated with surgical closure of the perforation, was discharged home 4 weeks later. The other was treated by insertion of a t-tube at laparotomy, but he died 40 days later from unexplained hemolytic anemia and generalized sepsis.

One patient had a wound dehiscence consequent to a leak at the site of the anastomosis. The anastomosis was revised and the child was subsequently discharged home.

Table 2 Details about the management and outcome of surgical complications following ITx according to the year of transplant

Year of Tx	No. of Tx/y	Type of graft	Complication	Days post Tx	Management	Result
1994	n = 1	Reduced LSBTx	Spontaneous bowel perforation+gastric perforation	28	Laparotomy and drainage	Died [a]
1996	n = 1	Full size ISBTx	Bowel obstruction	79	Laparotomy and internal hernia repair	Died
1998	n = 5	Reduced LSBTx	Spontaneous bowel perforation	9	Laparotomy and drainage	Discharged home
1999	n = 4	Reduced LSBTx	Recipient duodenal leak	6	Laparotomy and drainage	Discharged home
1999		Reduced LSBTx	Bowel obstruction	7	Laparotomy	Discharged home
1999		Full size ISBTx	Spontaneous bowel perforation	25	Laparotomy and drainage	Died [a]
1999		Reduced LSBTx	Bowel obstruction	8	Laparotomy and ileostomy prolapse repair	Discharged home
2000	n = 4	Reduced LSBTx	Graft duodenal leak	23	Laparotomy and drainage	Discharged home
2000		Reduced LSBTx	Abdominal Compartment syndrome	3	Laparotomy	Died [a]
2001	n = 4	Reduced LSBTx	Abdominal Compartment syndrome	9	Laparotomy	Discharged home
2001		Reduced LSBTx	Intra-abdominal Hematoma	11	Laparotomy and drainage of haematoma	Discharged home
2001		Full size LSBTx	Bowel obstruction	41	Laparotomy	Discharged home
2004	n = 6	Full size LSBTx	Abdominal Compartment syndrome	3	Laparotomy	Died [a]
2004		Whole LSBTx	Abdominal compartment syndrome	1	Laparotomy and decompression	Discharged home
2004		Whole LSBTx	Pancreatic leak	10	Conservative management	Discharged home
2004		Full size LSBTx	Graft duodenal leak	47	Laparotomy and drainage	Died [a]
2004		Full size LSBTx	Graft duodenal leak	30	Laparotomy and drainage	Discharged home
2005	n = 10	Full size LSBTx	Spontaneous bowel perforation	7	Laparotomy and drainage	Died [a]
2005		Reduced LSBTx	Pancreatic leak	16	Conservative management	Died
2005		Reduced LSBTx	Primary non-function	2	Laparotomy	Died [a]
2006	n = 4	Reduced LSBTx	Failure of staged closure of the abdominal wall	22	Treatment of wound sepsis and skin grafting	Discharged home
2006		Reduced LSBTx	Sub-acute bowel obstruction	115	Laparotomy and stoma refashioned	Discharged home
2006		Reduced LSBTx	Wound dehiscence due to pancreatic leak	14	Laparotomy	Discharged home
			Anastomotic leak	26	Refashioning of anastomosis	
2006		Reduced LSBTx	Portacaval thrombosis	Intraop	Thrombectomy	Died [a]
			Recipient duodenal perforation	11		
2007	n = 5	Reduced LSBTx	Wound dehiscence	12	Laparotomy+replacement of patch	Discharged home
			Portacaval thrombosis	D180	Dilatation by interventional radiologist	
2007		Reduced LSBTx	Sub-acute bowel obstruction	160	Laparotomy, resection, and anastomosis	Discharged home

ISBTx, Isolated small bowel transplantation; LSBTx, liver and small bowel transplantation.
[a] Children who died due to events directly related to surgical complications.

None of the bowel perforations were associated with CMV infection.

2.3. Subacute bowel obstruction (n = 6, all alive)

Six children (22%) had laparotomies for presumed acute/subacute bowel obstruction (Table 2). In 1 patient, an internal hernia was reduced and no bowel resection was needed. In 2 children, there was a suspicion that the bowel obstruction was secondary to ileostomy prolapse. The stomas were revised with resolution of symptoms. In the other 3 cases, no cause for bowel obstruction or other pathology was identified.

2.4. Abdominal compartment syndrome (n = 4, 2 alive)

Of the 29 children with emergency complications, 4 children had emergency laparotomies for abdominal compartment syndrome, 2 of whom died in 2004 (Table 2). These children had primary abdominal closure. From 2005 in children with recipient to donor weight mismatch with the

introduction of staged abdominal closure (n = 15), no further episode of abdominal compartment syndrome (ACS) was observed in children with staged abdominal closure.

2.5. Pancreatic fluid collection (n = 3, 2 alive)

Three children with composite liver and small bowel grafts (all 3 with reduced size livers) developed a pancreatic fluid collection from the donor's pancreatic head transplanted with the duodenum which was manifested clinically by increased nasogastric fluid losses (Table 2). None of these collections became infected. All were treated with percutaneous drainage and resolved within 10 to 12 weeks post ITx.

2.6. Other complications

Two children developed portacaval thrombosis (Table 2): 1 at the time of the operation, which was treated and did not recur, and the other identified on follow-up for investigation of persistently low albumin. Both the children died, but the cause of death was not directly related to the portacaval thrombosis. One patient had an emergency operation for continued intra-abdominal hemorrhage from vascularized adhesions on the day following transplant. One patient required emergency laparotomy for persistent acidosis and ionotropic support. There was patchy infarction of the graft and despite an attempt at resection deterioration continued. The most likely cause was thought to be primary nonfunction of the graft.

3. Discussion

Surgical complications occurred in 59% of the children following ITx and the main complications associated with significant morbidity and mortality were bowel perforation and ACS. During the study period, potential causes of these complications were recognized and our surgical approach modified resulting in an apparent reduction in morbidity and mortality.

The incidence, cause, and management of surgical complications associated with ITx in the transplant literature have not been widely reported. Reyes et al has documented 5 cases of vascular thrombosis and 10 cases of perforation amongst 58 ITx [8]. The Intestinal Transplant Registry reports that in children thrombosis/ischemia, or other technical complications, have led to death in 4% and 5% of cases, respectively. Two vascular thrombosis were identified at the portacaval shunt but none contributed to death.

The use of steroids and viral infections are thought to be contributory factors in intestinal perforation following isolated liver transplantation but no definite evidence exists [9,10]. In the 10 cases of perforation documented by Reyes et al [8], 4 children had intestinal perforation and 6 children had anastomotic leaks, but the exact site of the leaks is not described. In the 49 intestinal transplants performed in our programme, anastomotic leak was observed in 1 child, which was treated with refashioning of the anastomosis. In children with spontaneous bowel perforation, there was no correlation with treatment for acute rejection or viral infections before the perforation. It is probable that the method of procurement, handling of the graft and preservation injury may also be contributing factors when the perforation site is in the graft and that the need for using electrocoagulation extensively when dissecting and preparing the abdomen of these multioperated, debilitated children may be a contributing factor for perforation on recipient native digestive sites. A high index of clinical suspicion is necessary to diagnose early SBP as reported by Vilca et al [9] and Beierle et al [10] and changes in clinical parameters such as abdominal distension or reduction in the stomal output can be early signs. It is important to note that none of our children had pneumoperitoneum or other signs of peritonitis such as fever, marked abdominal tenderness, and leukocytosis. These signs were probably masked by the high dose of steroids used in the postoperative period. Careful and meticulous investigations with ultrasound scans, contrast studies, and computed tomographic scans may be necessary. Early second look operations may be needed to exclude SBP in high-risk children with minimal signs [11]. If a site of perforation is identified, the use of a T-tube as a means of controlled decompression of the bowel has been a successful technique in our experience. Primary suture closure of bowel in a very contaminated field and in an immune suppressed patient is not recommended, except may be for very early perforations. It is essential to identify the site of perforation at these laparotomies to be able to control sepsis but this may be surprisingly difficult and methylene blue dye instilled into the proximal intestinal lumen may be of some assistance in demonstrating the site of perforation. In 2 children, we were unable to identify the perforation and both these children died from sepsis.

Perforation of the graft duodenal stump was most likely due to the technique of CLITx procurement as then practiced at our center. In the past, the duodenum was transected within its first portion, then the gastroduodenal artery was divided and the pancreas was divided at the junction between the head and body, and the donor bowel was procured. At present, the gastroduodenal artery is carefully preserved in all CLITx cases with transection at the level next to the pylorus and the duodenopyloric junction is closed in 2 layers: this minimizes the risk of ischemia to the duodenum. Since the introduction of this technique, no graft duodenal stump leaks have been observed.

Three children developed a pancreatic fluid collection presumably from the cut surface of the donor pancreas. Kato et al [12] has reported that transplanting the whole pancreas rather than the head can prevent this complication. In our last 4 children transplanted, we have included the whole pancreas and none of these children developed a pancreatic leak.

In our early experience of 3 children with pseudoobstruction or gastric dysmotility, 2 proximal anastomoses were performed: first, the recipient's duodenum/jejunum to the graft's jejunum and the second one joining the graft's jejunum to recipient's stomach (gastrojejunostomy). The second anastomosis was performed to aid gastric emptying. However, it was difficult to establish feeding due to poor gastric emptying in a fourth child where a gastro-jejunostomy was fashioned as described above, which contributed to the development of intestinal failure associated liver disease and eventual death. In children with foregut dysmotility, it is now our practice to perform a subtotal gastrectomy on the recipient and either a gastrojejunostomy or if the stomach has been procured as a composite multivisceral graft to anastomose the graft stomach to the upper third of the recipient's with a Heineke-Mickulicz pyloroplasty to advance gastric emptying. The recipient's pancreas, spleen, and duodenum were left with native venous drainage via a portacaval anastomosis. Other centers are performing the "clean sweep" technique, whereby all the intra-abdominal organs (spleen, 2 thirds of the stomach, duodenum, pancreas, small and large bowel) are removed [4,13]. After the evisceration of the abdomen and subtotal gastrectomy, the anastomosis is performed with the graft stomach or jejunum.

In summary, preservation of gastroduodenal artery at the time of organ procurement, closure of the abdomen without any tension, and high index of suspicion for surgical complications especially perforation of the intestine with early second look laparotomy are essential surgical strategies. We conclude that the challenges of intestinal transplant surgery for young recipients with a contracted abdominal domain have demanded constant surgical innovation and a vigilant appreciation of new patterns of complications.

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