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Pediatric small bowel transplantation: A single-center experience from Turkey

INTESTINE

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ABSTRACT

Background/Aims: Small bowel transplantation (SBTx) is a treatment option for patients with serious parenteral nutrition-related problems in intestinal failure. İzmir Tepecik Training Research Hospital Organ Transplantation Center is still the only pediatric intestinal transplant center in Turkey.

Materials and Methods: This study was approved by the local ethics committee. Patients' data were analyzed from the medical charts and the hospital digital database. Seven isolated SBTxs were performed in six children between 2010 and 2016.

Results: One jejunal segment and six partial jejuno-ileal segments were used for seven transplants. All grafts were retrieved from deceased donors (one child and six adult donors). The six recipients had a mean age of 8.8±6.9 years (9 months to 17 years; M: 4, F: 2). The mean follow-up period of patients was 727±848 (34 to 1950) days. Acute cellular rejection (ACR) rates were 57% (n: 4) in the first 2 months. Graft loss due to severe ACR was seen in one patient. Central line-associated fungal (n: 3, 42%) and bacterial infections (n: 3, 42%) were seen in the first 2 months. Two Epstein-Barr virus (EBV) infections were recorded between 3 and 8 months in two patients. Our 1-year patient and graft survival rates were 71% and 71%, respectively.

Conclusion: SBTx has become a treatment modality for patients with intestinal failures. Management of ACR and infections are still challenging problems in SBTx. Appropriate-sized cadaveric donors are very limited in Turkey for pediatric intestinal transplantation candidates. Although the number of SBTxs performed was small, this study shows promising results.

Keywords: Small bowel transplantation, pediatria

INTRODUCTION

The first successful isolated small bowel transplant procedures were reported by Deltz et al. (1), Goulet et al. (2), and Starzl et al. (3) during 1989-1991. Today, small bowel transplantation (SBTx) is performed in many institutions, particularly in the USA (4). The first pediatric SBTx in Turkey was performed at our institution in 2010. Our institution is still the only pediatric intestinal transplant center in Turkey. By 2016, isolated SBTx had been performed on 18 adults and six pediatric patients in our transplant center. The number of pediatric patients with intestinal failure has increased due to advances in neonatal intensive care support and the increase in the number of premature births. SBTx is required in cases with unsuccessful intestinal rehabilitation such as some intractable diarrhea, total intestinal aganglionosis, gas-

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troschisis, and ultra-short segment short bowel syndrome. Although the number of patients who require SBTx is increasing, organ supply is still limited, particularly for the pediatric population. Because of this, we had to perform SBTx from deceased adult donors in all cases except one.

Intestinal transplantation is the treatment option for patients with serious parenteral nutrition-related problems in intestinal failure. Due to the complexity of the procedure, prospective studies could not be conducted. In our opinion, all reports on SBTx are very important. Here we report our seven pediatric intestinal transplant experiences in detail.

MATERIALS AND METHODS

This study was approved by the local ethics committee. Patients' data were analyzed from medical files and the hospital digital database. Informed consent was received from all patients. Seven isolated SBTxs were performed in six children between 2010 and 2016. Biochemistry, microbiological, and immunological analyses were evaluated for all patients. A conventional vaccine program was performed in all patients before transplantation. Pre-transplant imaging included comprehensive computed tomography scans, angiograms, and radiographic intestinal studies. Liver and renal functions were carefully evaluated. Intestinal grafts were obtained from donors with identical blood groups. Before recovery, complement-dependent cytotoxicity and flow cytometric cross-match were performed. All cross-match analyses were negative in all patients.

Prophylactic treatments and Immunosuppression protocols

Prophylactic treatment consisting of antifungal (fluconazole or amphotericin B), anti-bacterial (vancomycin or teicoplanin and piperacillin-tazobactam), and anti-viral (ganciclovir) therapies were introduced for all patients. Valganciclovir and nystatin prophylaxes were extended to 1 year.

The immunosuppression protocol for induction therapy was rabbit antithymocyte globulin (rATG-Fresenius®, 10 mg/kg) and a steroid (10 mg/kg). After transplantation, intravenous tacrolimus was used until bowel motility was observed. Tacrolimus (Prograf TM), with an initial dose of 15–20 µng/mL, was tapered after 2 months to 8–10 µng/mL, and sirolimus or everolimus was added for immunosuppression therapy. A low-dose oral steroid was used in the following 6–9 months. In the post-transplant second month, sirolimus or everolimus (3–8 µng/mL) was added. Between 2009 and 2012, autologous bone marrow mesenchymal stem cell (BMSC) therapy was added to our protocol for patients undergoing SBTx. Our BMSC procedure was previously described elsewhere (5). BMSCs were used only for the first three pediatric transplants before 2012.

High-dose steroids, rATG, and/or intravenous immunoglobulin (IVIG) were used in the acute cellular rejection (ACR) period. TNF-alfa blocker (Remicade®, Janssen Biotech Inc.; PA, USA) was used in chronic rejections.

Organ recovery procedure

We used the University of Wisconsin (UW™) solution for organ perfusion. After removing the small bowel, the graft was re-perfused with UW solution on the back table before cold preservation. We used only jejuno-ileal grafts without the right colon.

Surgical procedure

Before the transplant procedure, to create enough space, some failed organs were removed and major vascular vessels were obtained for the graft placement. The graft artery was anastomosed to the infrarenal aorta and the graft vein was drained to the infrarenal vena cava. Extension graft was not used for the vascular anastomosis. Duodenojejunostomy was performed and a feeding tube was placed into the graft via gastrostomy for postoperative nutrition. For distal side reconstruction, a simple ostomy was preferred. Ostomy takedown was performed after one year by anastomosis with recipient remnant colon. As needed, the graft was shortened on the jejunal side for the abdominal closure procedure.

Graft monitoring via endoscopy was performed routinely two times in the first 2 weeks, then followed at 1-week intervals until the second month.

Statistical methods

For discrete and continuous variables, descriptive statistics (mean, standard deviation, median, minimum value, maximum value, and percentile) were given. The survival rates were obtained using Kaplan–Meier curves. Patient survival was calculated from the transplantation date until the patient's death or the end of the study period. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc.; NY, USA) version 22.

RESULTS

Recipients

Ten patients were enrolled for SBTx between 2010 and 2016. Two patients died on the waiting list due to catheter-related infections (one fungal, one bacterial) and currently, two patients are on the waiting list. One patient underwent re-transplantation after graft loss due to chronic rejection. Demographic findings of the six recipients were: mean ages 8.8±6.9 (9 months to 17 years; M: 4, F: 2). Mean follow-up was 727±848 (34 to 1950) days. All patients were parenteral nutrition (PN) dependent and stayed in hospital before the transplantation. Pre and postoperative median hospital stay were 172 and 68 days, respectively. Indications for SBTx were the presence of recurrent bloodstream derived sepsis (n=6), graft loss (n=1), and loss of central venous access (n=4). Liver biopsy was performed in two recipients and mild fibrosis was found. Three patients received BMSCs besides induction therapy; two recipients died from them. One patient died due to post-transplant lymphoproliferative disease (PTLD) and sepsis on the 14th month. Another patient underwent re-laparotomy due to graft vascular thrombosis in the early postoperative period, the patient died

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on the waiting list for re-transplantation. The third patient lost the graft due to chronic rejection at the 45th month. The patient characteristics are shown in Table 1. The patient survival rate of seven recipients was 71% in the first year.

Grafts

All grafts were retrieved from deceased donors (one child and 6 adult donors). One jejunal segment and 6 partial jejuno-ileal segments were used for seven transplantations. ACR rates were 57% (n: 4) in the first 2 months. Graft loss due to severe ACR was seen in one patient. Other rejection attacks were mild. Chronic rejection was seen in one patient (14%) and resulted in graft loss in the 45th month despite the use of TNF-blocker treatment. The graft survival rate in the first year was 71%.

Postoperative complications

Median duration in the intensive care unit was 4 days (min 1, max 81). Re-laparotomy was required in two patients (28%). Vascular thrombosis was seen in one patient (at day 3), and obstruction due to rejection was determined in another patient (at day 30). No abdominal compartment syndrome was observed. Encephalopathy was recorded in one patient due to posterior reversible encephalopathy syndrome (PRES).

Infections

Central line associated bacterial and fungal infections were commonly seen prior to PN free time. Central line associated fungal (n: 3, 42%) and bacterial infections (n: 3, 42%) were seen in the first 2 months. Two Epstein-Barr virus (EBV) infections were recorded between 3 and 8 months in two patients. EBV-related PTLD were determined at tissue biopsy (CD 20+ and CD 79a+) in one patient. Persistent gastrointestinal hemorrhage was observed from multiple ulcers after the third dose of rituximab therapy. No recovery was seen despite IVIG and Rituximab (MAB-THERA™) therapy. Invasive cytomegalovirus (CMV) infection was seen at 39 months in one patient. Viral DNA were detected in sera and inclusion bodies were seen in tissue biopsy. She was treated with iv ganciclovir.

Other complications on follow-up

Renal dysfunction occurred in three cases (50%). Renal failure was observed in one patient after one year (16%). In this patient, calcineurin-associated tubulopathy was detected in the renal biopsy.

Lymphedema was observed in one patient on sirolimus therapy at 11 months. Lymphatics obstructions were determined at lymphoscintigraphy. Vascular occlusion was not observed in the imaging examination. Sirolimus therapy was stopped as we considered that it might be responsible for the existing clinical condition. Lymphedema reduced after the cessation of sirolimus, but the patient did not completely recover.

DISCUSSION

The International Transplant Registry reports shows that about 100 to 120 pediatric intestine transplants are performed annually (6). We have a lack of data for the exact number of patients who need intestinal transplantation in Turkey. According to the multicenter European survey conducted in 2001, the estimated incidence of children on home parenteral nutrition was 2–6.8 per million people (7). When this data is adapted to the Turkish population, the estimated incidence of children on parenteral nutrition is about 150–500 annually.

Surveillance endoscopic evaluation is the most important tool for the determination of ACR. ACR is determined in the first 3 months. The historic incidence of ACR (80%) has improved to 20–50% (6,8-11). The level of ACR has declined following the use of rATG (4,12). We used rATG and steroids for induction therapy and our ACR rate was 57%.

Mesenchymal stem cells have the ability to inhibit T-cell proliferation in vitro and in vivo and to exert similar inhibitory effects on B, dendritic, and natural killer cells. It is used as a new stem cell therapy for autoimmune diseases, solid organ transplantation, and treatment of graft-versus-host disease (13-15). For reducing ACR, BMSC treatment was used in three patients. Mild ACRs were found in two patients who received BMSCs, but graft loss did not occur due to ACR in the early period.

The incidence of chronic rejection was reported at 10% to 15% and is the most common in the 22–67-month period (1,3). The mechanism of this type of rejection is not understood; hence, treatment is not well-defined. Re-transplantation is usually the

Table 2. Patient and donor characteristics

	Recipient age/gender	Recipient weight (kg)	Donor age/gender	Donor weight (kg)	Cause of intestinal failure
Patient 1	9 months/male	7	34 years/female	48	Waardenburg syndrome
Patient 2	12 years/female	39	27 years/male	49	Major traumatic injury
Patient 2 (re-transplant)	16 years/female	40	50 years/male	90	Graft loss
Patient 3	17 years/male	47	60 years/male	80	Malrotation
Patient 4	12 years/female	23	42 years/male	-	Malrotation
Patient 5	5 years/male	10	42 years/male	75	Waardenburg syndrome
Patient 6	6 months/male	6	3 years/female	15	Volvulus

Table 2. Patient and graft survival

	HLA Mm	CI time (minute)	BMSCs	GS (day)	PS (day)	Patient status	Cause of graft loss	Cause of death
Patient 1	6	420	+	415	415	Dead	PTLD	Sepsis
Patient 2	2	410	+	1500	1950	Alive	Chronic rejection	-
Patient 2 (Re-tx)	4	450	–	450	450	Alive	-	-
Patient 3	5	380	–	390	390	Alive	-	-
Patient 4	5	380	–	30	34	Dead	Acute rejection	Sepsis and MOF
Patient 5	5	340	–	300	300	Alive	-	-
Patient 6	5	255	+	3	51	Dead	Vascular thrombosis	Sepsis

Mm: mismatch; CI: cold ischemia; BMSCs: bone marrow mesenchymal stem cell; GS: graft survival; PS: patient survival; Re-tx: re-transplant; MOF: multiple organ failure; PTLD: post-transplant lymphoproliferative disease

only solution (10). We identified only one case of chronic rejection (14%), and the graft was removed due to failed treatment at the 45th month.

CMV and EBV infections are life-treating and cause graft loss in children with SBTx. The incidence of CMV infection was reported at about 14% to 25% (6,11). We encountered one case of invasive CMV infection, and it was treated by IV ganciclovir. There was a chronic rejection at the same time. Intensive anti-rejection treatment was used before the CMV infection. Re-transplantation was performed due to graft loss in this patient. In particular, in young children with SBTx, if anti-EBV IgG is negative in the pre-transplant assessment, the risk of PTLD increases (16,17). The incidence of EBV was reported to be 25–33% in pediatric SBTx during the first 6 months. The prevalence of PTLD was 16–17% in pediatric SBTx (11,18). The use of anti-T-cell antibodies has been considered as a risk factor (14). PTLD was seen in one patient (14%) 9 months post transplant under oral valganciclovir prophylaxis.

Kidney dysfunction secondary to immunosuppressive therapy in SBTx has been reported as 46% (19). Ojo et al. (20) reported that 21% of 5-year survivors of SBTx had chronic kidney disease. In our series, renal dysfunction occurred in three patients (50%) and chronic renal failure was observed in one patient (14%).

As in other solid organ transplants, m-Tor inhibitors were used in SBTx as an immunosuppressive therapy with corticosteroids and tacrolimus (11,21,22). Sirolimus-related lymphedema has been reported in organ transplantation (23). Lymphedema was seen in one of three patients using sirolimus, and a partial improvement was observed when treatment was stopped in this patient. Everolimus was given to two patients. It was well tolerated without any adverse effects.

The incidences of 1-year graft and patient survival were 75% and 79%, respectively, in 2007 (3). Nearly Dopazo et al. (12) reported that they performed 91 SBTxs for 74 children. One- and 5-year patient survival rates were 80% and 68%, respectively, and 1- and 5- year graft survival rates were 68% and 59%, respectively The 1-, 3-, and 5-year patient survival rates of 199 children who had transplants in Pittsburgh were 95%, 84%, and 77%, respectively, and 1-, 3-, and 5-years graft survival rates were 88%, 74%, and 58%, respectively (3). Our 1-year patient and graft survival rates were 71% and 71%, respectively.

Small bowel transplantation has become a potential treatment for patients with intestinal failure. ACR and infections are the main problems in SBTx.

In conclusion, appropriate-sized deceased donors for pediatric intestinal transplantation candidates are very limited in Turkey. Therefore, pediatric candidates have to wait for a long time on the transplant list. Despite this, we have performed SBTx from adult donors for pediatric patients, and this study shows acceptable and promising results.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İzmir Tepecik Training and Research Hospital (15 March 2016, No: 17).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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*CT and MB contributed equally to this paper.

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REFERENCES

1. Deltz E, Schroeder P, Gebhardt H, et al. Successful clinical small bowel transplantation: report of a case. Clin Transpl 1989; 3: 89-91.
2. Goulet O, Revillon Y, Jan D, et al. Small-bowel transplantation in children. Transplant Proc 1990; 22: 2499-500.
3. Starzl TE, Todo S, Tzakis A, et al. The many faces of multivisceral transplantation [review]. Surg Gynecol Obstet 1991; 172: 335-44. [Er-ratum in Surg Gynecol Obstet 1991; 173: 242.
4. Nayyar N, Mazariegos G, Ranganathan S, et al. Pediatric small bowel transplantation. Semin Pediatr Surg 2010; 19: 68-77. **[CrossRef]**
5 Doğan SM, Kılınç S, Kebapçı E, et al. Mesenchymal stem cell therapy in patients with small bowel transplantation: Single center experience. World J Gastroenterol 2014; 20: 8215-20. **[CrossRef]**
6. Mazariegos GV, Squires RH, Sindhi RK. Current Persipectives on Pediatric Small Bowel Transplantation. Current Gastroenterology Reports 2009: 11: 226-33. **[CrossRef]**
7. Van Gossum A, Vahedi K, Abdel Malik, et al. Espen-Han Workıng Group. Clinical social and rehabilitation status of long term home parenteral nutrition patients: Results of a European multicentere survey. Clin Nutr, 2001; 20: 205-10. **[CrossRef]**
8. Abu-Elmagd KM, Costa G, Bond GJ, et al. Evolution of the immunosuppressive strategies for the intestinal and multivisceral recipients with special reference to allograft immunity and achievement of partial tolerance. Transpl Int 2009; 22: 96-109. **[CrossRef]**
9. Ishii T, Mazariegos GV, Bueno J, Ohwada S, Reyes J. Exfoliative rejection after intestinal transplantation in children. Pediatr Transplant 2003; 7: 185-91. **[CrossRef]**
10. Avıtzor Y, Grant D. Intestine Transplantation in Children: Update 2010. Pediatr Clin North Am 2010; 57: 415-31. **[CrossRef]**
11. Moon J, Iyer K. Intestinal rehabilitation and transplantation for intestinal failure. Mt Sinai J Med 2012; 79: 256-66. **[CrossRef]**
12. Dopazo C, Gupte GL, Sharif K, et al. Combined Liver-Intestine Grafts Compared With Isolated Intestinal Transplantation in Children: A Single-Center Experience. Transplantation 2012; 94: 859-65. **[CrossRef]**
13. Kim N, Im K, Lim Jy, et al. Mesenchymal stem cells for the treatment and prevention of graft-versus-host disease: experiments and practice. Ann Hematol 2013; 92: 1295-308. **[CrossRef]**
14. Reinders ME, Rabelink TJ, De Fijter JW. The role of mesenchymal stromal cells in chronic transplant rejection after solid organ transplantation. Curr Opin Organ Transplant 2013; 18: 44-50. **[CrossRef]**
15. Tan J, Wu W, Xu X, et al. Induction therapy with autologous mesenchymal stem cells in living-related kidney transplants: a randomized controlled trial. JAMA 2012; 307: 1169-77. **[CrossRef]**
16. Talisetti A, Testa G, Holterman M, John E, Kecskes S, Benedetti E. Successful treatment of posttransplant lymphoproliferative disorder with removal of small bowel graft and subsequent second bowel transplantation. J Pediatr Gastroenterol Nutr 2005; 41: 354-6. **[CrossRef]**
17. Ramos E, Hernández F, Andres A, et al. Post-transplant lymphoproliferative disorders and other malignancies after pediatric intestinal transplantation: incidence, clinical features and outcome. Pediatr Transplant 2013; 17: 472-8. **[CrossRef]**
18. Yeh J, Ngo KD, Wozniak LJ, et al. Endoscopy Following Pediatric Intestinal Transplant. J Pediatr Gastroenterol Nutr 2015; 61: 636-40. **[CrossRef]**
19. Suzuki M, Mujtaba MA, Sharfuddın AA, et al. Risk factors for native kidney dysfunction in patients with abdominal multivisceral/small bowel transplantation. Clin Transplant 2012; 26: E351-358. **[CrossRef]**
20. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003; 349: 931-40. **[CrossRef]**
21. Macdonald AS. Use of mTOR inhibitors in human organ transplantation. Expert Rev Clin Immunol. 2007; 3: 423-36. **[CrossRef]**
22. Beduschi T, Garcia J, Lugo-Baruqui J, et al. Everolimus with low dose Tacrolimus in intestinal transplantation (abstract). Am J Transplant 2015; 15(Suppl 3).
23. Desai N, Heenan S, Mortimer PS. Sirolimus-associated lymphoedema: eight new cases and a proposed mechanism. Br J Derma tol 2009; 160: 1322-6. **[CrossRef]**