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LIVER TRANSPLANTATION IN PEDIATRIC PATIENTS UNDER 15-KG; DUCT-TO-DUCT VS. ROUX-EN-Y HEPATICOJEJUNOSTOMY BILIARY ANASTOMOSES

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Back ground. Liver transplantation is an effective treatment for acute or chronic liver failure and metabolic liver disease, which is associated with good quality of life in over 80 percent of recipients. We aimed to evaluate outcome of duct-to-duct vs. Roux-en-Y hepaticojejunostomy biliary anastomoses in pediatric liver transplant recipients below 15-kg. **Methods.** In this single-center retrospective study, all children less than 15 kg that have undergone liver transplantation at Nemazee Hospital Organ Transplant Center affiliated with Shiraz University of Medical Sciences from 2009 till 2019, were enrolled. Over a 10-yr period, 181 liver transplants were performed in patients with two techniques including duct-to-duct (Group 1) vs. Roux-en-Y hepaticojejunostomy biliary anastomoses (Group 2). All data was collected from patients' medical records, operative notes, and post-transplant follow up notes. Data was analyzed by SPSS software V21. **Results.** Overall, 94 patients had duct to duct anastomosis (group 1) and 87 cases had Roux-en-Y hepaticojejunostomy (group 2). The mean age of the patients was 2.46 ± 1.5. The most common underlying diseases was biliary atresia (32%). The most prevalent complication after the surgery was infection in both groups. cardiopulmonary problems were significantly higher in group 2 (24.1% vs 4.3%) ($p < 0.001$). The rate of infection was significantly higher in group 2, as well. **Conclusion.** Our study showed a relatively high rate of post-operative infection which was the most among patients who had undergone Roux-en-Y hepaticojejunostomy. Except from biliary complications which were mostly observed in DD group, other complications were more common among Roux-en-Y group.

Keywords: liver transplantation, duct-to-duct biliary reconstructions, Roux-en-Y hepaticojejunostomy, Biliary complications.

INTRODUCTION

Liver transplantation (LT) is an established curative therapy for acute or chronic liver failure or liver metabolic disease. Survival after LT has improved significantly in developed countries and this has increased the awareness of this treatment modality in the developing world. The development of newer immunosuppressive drugs, refinements in operative technique, improved organ preservation, advances in allied service specially anesthesia and intensive care have contributed to a dramatic improvement in the survival of these patients. It is essential to encourage both the child and the family to return to a normal life as far as possible. Most of the children who survive liver transplantation will achieve nutritional rehabilitation and a normal lifestyle. Most will enter puberty normally, and fertility is normal. Pediatric liver transplantation has been evolving over recent decades. The developments in reduced sized grafts and living donor liver transplants have significantly reduced mortality rates for pediatric patients suffering from end-stage liver disease [1, 2]. However, despite continuous improvements in surgical techniques, biliary complications including leakage from biliary radicals, anastomotic leaks, and strictures are still associated with significant morbidity and mortality occurring with an incidence of 10% to 50% [3, 4]. Although transplant-related biliary complications are not associated with decreased patient survival in pediatrics, these complications do cause considerable morbidity, increased length of stay, need for increased operative and non-operative interventions, and occasionally re-transplantation. Historically, the biliary anastomosis has been termed the Achilles heel of orthotopic liver transplantation [5]. Complications such as leakage, stricture, fistula, infection, and cast formation led to the evolution of new technical methods. Early biliary reconstructions were performed using loop choledochojejunostomy and Roux-en-Y hepaticojejunostomy,

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as well as using the gallbladder as a conduit. In the 1980s, duct-to-duct choledocho-choledochostomy drainage over a T-tube became the most popular technique. During the past two decades, duct-to-duct anastomosis without a T-tube has become the primary method of reconstruction. With the advent of living donor liver transplantation in the 1990s, reconstruction without enteric anastomosis has been performed (5). Although Roux-en-Y hepaticojejunostomy has been the standard procedure in LDLT, the disadvantages of this technique are a comparatively long operative time and higher risk of contamination due to construction of the Roux-en-Y limb. Theoretically, Duct-to-duct biliary reconstruction has some benefits when it is compared with the Roux-en-Y procedure, namely no manipulation of the gastrointestinal tract, a shorter operative time and allowing for easy endoscopic access to the anastomotic site if complications arise. It is the standard technique of choice for biliary anastomosis in cadaveric liver transplantation. When the duct-to-duct technique can be employed for LDLT, an extra-intestinal anastomosis can be avoided, the continuity is more physiologic than that of RYHJ, and preservation of the sphincter function of the lower bile duct may reduce the risk of enteric reflux into the biliary tract. Also, Duct-to-duct biliary reconstruction is mostly the standard technique in adult liver transplantation. On the other hand, the predominance of biliary atresia along with the technical challenges related to the small size and fragility of recipient's duct in the pediatric age population have made Roux-en-Y hepaticojejunostomy far more common. There are still a lot to learn and there are future challenges to improve liver transplantation techniques. The evolution of the field of liver transplantation has resulted in improved patient outcomes. A paucity of data exists for the outcomes of these two techniques [10]. The aim of this study was to compare the outcomes of duct-to-duct vs. Roux-en-Y hepaticojejunostomy biliary anastomoses in pediatric liver transplant recipients below 15-kg.

METHODS

In this single-center retrospective study, all children less than 15 kg that have undergone liver transplantation at Nemazee Hospital Organ Transplant Center affiliated with Shiraz University of Medical Sciences from 2009 till 2019, were enrolled. Over a 10-yr period, 181 liver transplants were performed in patients with two techniques including duct-to-duct (Group 1) vs. Roux-en-Y hepaticojejunostomy biliary anastomoses (Group 2). The electronic medical record was used to collect patients' characteristics including age, medical history, details of transplantation surgery, and postoperative hospital course. Postoperative information collected included patient and graft survival. Data were expressed as means ± standard deviation. Fisher's exact test, unpaired *t* tests, and the log-rank test were used for statistical analysis. *P* values less than 0.05 were regarded as significant. All liver recipients, of a whole or partial liver graft, weighting less than 15 kg were included. All data were collected from patients' medical records, operative notes, and post-transplant follow up notes. Demographic data such as age, sex, weight, primary diagnosis, PELD (pediatric end-stage liver disease) score, previous biliary tract surgeries, type and weight of graft, type of donor, date of transplantation, graft ischemia time, operative time, biliary and vascular complications were collected. Patients were divided into two groups based on the type of biliary anastomosis done during surgery: duct-to-duct biliary reconstruction and Roux-en-Y hepaticojejunostomy biliary reconstruction. Duct-to-duct biliary anastomosis was preferably performed whenever it was thought to be technically feasible by the operating surgeon. Biliary complications including biliary leaks, strictures, or development of cholangitis were recorded. Biliary leaks from anastomotic sites were diagnosed based on cholangiograms and were considered as significant complications if any further intervention was deemed to be necessary. Biliary strictures were diagnosed based on cholestatic trend of liver enzymes suggestive of a stricture in addition to a confirmatory cholangiogram demonstrating the presence of a stricture. Cholangitis was considered in any patient developing fever or raised level of white cell count with elevated bilirubin. Vascular complications consisted of hepatic artery thrombosis or stricture. Both vascular complications were initially diagnosed by Doppler ultrasound with further confirmation of arterial stenosis by angiogram. Mortality rate of two groups were also considered. Student's t-test and Pearson's chi-square were primarily used to compare both groups. Further statistical analysis was performed using Fisher's exact test with the Freeman–Halton extension when appropriate.

RESULTS

Pre-operative characteristics of the patients

Overall, 94 patients had duct to duct anastomosis (group 1) from which 46 expired and 87 cases had Roux-en-Y hepaticojejunostomy (group 2) from which 43 cases passed away. The mean age of the patients was 2.468 ± 1.5711 year (0.5–10) and their mean weight was 10.403 ± 2.5501 Kg (4–15). The most common underlying diseases were biliary atresia (32%), PFIC (17.1%) tyrosinemia (16%) and Crigler-Najjar (10.5%). The most common complication before the surgery was ascites with a prevalence of 8.8% in our patients. The mean PELD scores in group 1 and 2 before surgery were 15.19 ± 8.9 and 19.64 ± 6.9 respectively. Out of 94 patients in group 1, 44 underwent partial liver transplantation, 23 experienced split transplantation and 27 had whole organ transplantation. The corresponding numbers in the group 2 were 61, 13, and 12 patients. The most common donor relation

in group one was DD and in group 2, mothers were the most donors. The complete pre-operative characteristics of patients are listed in table 1.

Post-operative characteristics

Prednisolone and Tacrolimus were the most required immunosuppressive used in both groups. Our data showed that the patients who need Prednisolone, Tacrolimus and Mycophenolate in group 1 were significantly more than group 2 (P value <0.05). The most prevalent complication after the surgery was infection in both groups. cardiopulmonary problems were significantly higher in group 2 (24.1% vs 4.3%) ($p < 0.001$). The rate of infection was significantly higher in group 2, as well. Although the rate of biliary complications was higher in the group 1, this difference was not statistically significant. The least needed re-operation was drainage of the collection and the most prevalent surgical procedures were ERCP and Roux-en-Y Hepaticojejunostomy after Duct to Duct, both with the prevalence of 7%. The most common causes of death were infection (9.2%), sepsis (8.3%) and rejection (6.1%) (table 2).

DISCUSSION

Despite the fact that the most common type of biliary anastomosis is duct to duct hepaticojejunostomy biliary anastomosis, there is still discussion about the safety of this method in pediatrics [11–13]. Some studies suggested Roux-en-Y hepaticojejunostomy as the method of choice as it is associated with lower stricture formation and higher graft survival. There are not enough reports on using these methods in children. As the most prevalent type of complication followed by this procedure is biliary complication, some studies focused on this type of complication. The biliary complication rate after optimizing duct to duct anastomosis has been reported to be around 28.6–47.7% in children based on some earlier small reports [14, 15]. Meanwhile, the corresponding rate for adults was reported 26.9% [16]. However, A more recent study indicated a 12.7% rate of biliary complication in a group of 298 LDLT pediatrics, 75% of which had

Table 1

Pre-operative characteristics of patients

Pre-operative characteristics		Group 1	Group 2
Male/Female		54/40	47/40
Age		2.829 ± 1.5551 (0.5–8)	2.078 ± 1.5018 (0.5–10)
Weight		11.178 ± 2.3343 (6–15)	9.567 ± 2.5209 (4–15)
PELD score		15.19 ± 8.9	19.64 ± 6.9
Donor Relation	Mother	26	29
	Father	16	27
	DD	49	25
	Uncle or Aunt	3	6
Graft type	Partial	44	61
	Split	23	13
	Whole organ	27	12
Underlying disease	PFIC	31 (17.1%)	
	Intrahepatic Cholestasis	2 (1.1%)	
	Crigler-Najjar	19 (10.5%)	
	Tyrosinemia	29 (16%)	
	Biliary Atresia	58 (32%)	
	Cryptogenic	9 (5%)	
	HCC	3 (1.7%)	
	Autoimmune Hepatitis	4 (2.2%)	
	Hypercholesterolemia	6 (3.3%)	
	Neonatal Hepatitis	6 (3.3%)	
	Choledochal Cyst	2 (1.2%)	
	Other*	12 (6.6%)	
Complications	Encephalopathy	3 (1.7%)	
	GI bleeding	4 (2.2%)	
	Ascites	16 (8.8%)	
	Hepatorenal Sx	1 (0.6%)	
	Hepatopulmonary sx	1 (0.6%)	

Note. * Other: the underlying diseases which contain problems like hepatitis, Caroli, glycogen storage disease, Hepatoblastoma, Alagille syndrome, MSUD and Methylmalonic acidemia.

undergone duct to duct anastomosis [17]. The prevalence of this complication was lower in patients who have undergone Roux-en-Y surgery (12.6%) compared with the duct to duct anastomosis group (20.2%). However, this difference was not significant.

In this study, in addition to biliary complication, which is the most common complication discussed in previous studies, other complications related to these procedures were also discussed and compared. The most prevalent complication in both techniques was infection. Despite the fact that most of our immunosuppressive agents were mostly used in the DD group, the rate of infection was higher among Roux-en-Y patients which can be related to the higher length of the operation time. Our study indicated that around 38% OF DD group and 56% of Roux-en-Y group developed infection after surgery. More specifically, about 15% of our patients died either from infection or sepsis. Acute and chronic rejections both showed higher rates among DD group. However, these differences were not significant. One of the most common vascular complications in liver transplant patients is Hepatic artery thrombosis (HAT), which has been identified as a cause of biliary complication. Some studies have shown that the incidence of HAT in Roux-en-Y reconstruction was higher than DD anastomosis in adult liver transplantation and have identified Roux-en-Y

Table 2

Post-operative characteristics of patients

Post-operative characteristics		Group 1	Group 2
Immunosuppressive treatment requirement	Prednisolone	91 (96.8)	70 (80.5)
	Cyclosporine	3 (3.2)	4 (4.6)
	Tacrolimus	87 (92.6)	67 (77)
	Mycophenolate	22 (23.4)	9 (10.3)
	Sirolimus	1 (1.1)	1 (1.1)
Complications	Biliary Complications	19 (20.2)	11 (12.6)
	Vascular Complications	9 (9.6)	11 (12.6)
	Infection	36 (38.3%)	49 (56.3%)
	Ascites	3 (3.2%)	7 (8%)
	Convulsions	4 (4.35)	8 (9.2%)
	Renal problems	2 (2.1%)	6 (6.9%)
	Cardiopulmonary problem	4 (4.3%)	21 (24.1%)
	Acute Rejection	23 (24.5%)	16 (18.4%)
	Chronic rejection	2 (2.1%)	1 (1.1%)
Bile duct dilatation requirement	No Need	167 (92.3%)	
	PTC	4 (2.2%)	
	ERCP	7 (3.9%)	
	Missing	3 (1.7%)	
Need for surgical repair	No Need	171 (94.5%)	
	Duct to Duct repair	1 (0.6%)	
	Roux-en-Y Hepaticojejunostomy after Duct to Duct	7 (3.9%)	
	Missing	2 (1.1%)	
Need for drainage of the collection	No Need	179 (98.9%)	
	Missing	2 (1.1%)	
Cause of death	Bleeding	3 (1.7%)	
	PNF	6 (3.3%)	
	Liver Necrosis	2 (1.1%)	
	Pulmonary Problems	5 (2.8%)	
	Rejection	11 (6.1%)	
	Sepsis	15 (8.3%)	
	Renal Failure	3 (1.7%)	
	Convulsion	1 (6%)	
	Pneumonia	7 (3.9%)	
	Cardiac arrest	9 (5%)	
	Infection	4 (9.2%)	
	PTLD	9 (5%)	
	Other	12 (6.6%)	
	Missing	4 (2.2%)	

surgery as a risk factor for HAT [18]. Studies in children have also found the higher rates of HAT in Roux-en-Y reconstruction (9%) than its prevalence in DD anastomosis group (3.3%), which was consistent with our study [19]. The prevalence of vascular complications in Roux-en-Y surgery group was 12.6% compared with 9.6% in DD group. One of the reasons that might cause this difference is that Roux-en-Y construction leads to compression of the arterial anastomosis [19]. The cardiopulmonary complication was also one of the significant complications in this study that has been less noticed in previous studies. Some studies have shown a prevalence of respiratory failure following Roux-en-Y hepaticojejunostomy is about 10% [20]. Kawachi et al. also showed in their study that one patient (10%) had idiopathic cardiac failure following Roux-en-Y surgery and pulmonary complications observed in one patient (10%) who have undergone duct to duct anastomosis [21]. In this study, cardiopulmonary complications were higher in Roux-en-Y surgery group (24.1%) compared with the duct to duct anastomosis group (4.3%). This difference was statistically significant ($p < 0.001$). Our finding is supported by Stilling et al's study on 139 adult patients who had bile duct injury during cholecystectomy and underwent repaired Roux-en-Y hepaticojejunostomy. They reported that 12% of patients developed cardiopulmonary complications in less than a month after surgery [22]. S.V. McDiarmid et al. in 2003 investigated the liver transplantation in children. Their study revealed that a long-term outlook for children receiving liver transplantation is likely to be limited by donor supply, the side effects of immunosuppressive drugs and the potential development of post transplantation lymphoproliferative disease or other tumors [1]. T. Kimura et al. in their study which was performed in 2006 about Feasibility of duct-to-duct biliary reconstruction in pediatric living related liver transplantation (Report of three cases) demonstrated that duct-to-duct biliary reconstructions in pediatric seemed to be feasible and safe [6]. Y. Shirouzu et al. compared the outcome of Roux-en-Y hepaticojejunostomy and duct-to-duct anastomosis in 2008. Their results showed that their surgical technique using DD in recipients weighing no more than 10 kg produced excellent outcomes with a low incidence of biliary complications, including leakage and stricture [2].

CONCLUSION

Our study showed a relatively high rate of post-operative infection which was the most among patients who had undergone Roux-en-Y hepaticojejunostomy. Except from biliary complications which were mostly observed in DD group, other complications were more common among Roux-en-Y group.

The authors declare no conflict of interest.

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