Pediatric Liver Transplantation: Our Experiences

Pediatrik Karaciğer Transplantasyonu: Tek Merkez Deneyimi

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ABSTRACT

Objective: The aim of our study was to evaluate our liver transplant pediatric patients and to report our experience in the complications and the long-term follow-up results.

Materials and Methods: Patients between the ages of 0 and 18 years, who had liver transplantation in the organ transplantation center of our university hospital between 1997 and 2016, were included in the study. The age, sex, indications for the liver transplantation, complications after the transplantation, and long-term follow-up findings were retrospectively evaluated. The obtained results were analyzed with statistical methods.

Results: In our organ transplantation center, 62 pediatric liver transplantations were carried out since 1997. The mean age of our patients was 7.3 years (6.5 months–17 years). The 4 most common reasons for liver transplantation were: Wilson's disease (n=10; 16.3%), biliary atresia (n=9; 14.5%), progressive familial intrahepatic cholestasis (n=8; 12.9%), and cryptogenic cirrhosis (n=7; 11.3%). The mortality rate after transplantation was 19.6% (12 of the total 62 patients). The observed acute and chronic rejection rates were 34% and 4.9%, respectively. Thrombosis (9.6%) was observed in the hepatic artery (4.8%) and portal vein (4.8%). Bile leakage and biliary stricture rates were 31% and 11%, respectively. 1-year and 5-year survival rates of our patients were 87% and 84%, respectively.

Conclusion: The morbidity and mortality rates in our organ transplantation center, regarding pediatric liver transplantations, are consistent with the literature.

Keywords: Child, liver transplantation, liver failure

ÖZ

Amaç: Çalışmamızın amacı pediatrik karaciğer nakilli hastalarımızı değerlendirerek deneyim, komplikasyonlar ve uzun süreli izlem sonuçlarımızı bildirmektir.

Gereç ve Yöntem: Üniversite hastanesi organ nakil merkezinde 1997 ile 2016 yılları arasında karaciğer nakli yapılmış 0-18 yaş arasındaki hastalar ile çalışma yapılmıştır. Hastaların yaş, cinsiyet, karaciğer nakil endikasyonu, nakil sonrası komplikasyonlar ve uzun süreli izlem bulguları retrospektif olarak değerlendirilmiştir. Elde edilen sonuçların istatistiksel analizi yapılmıştır.

Bulgular: 1997'den bu yana organ nakli ünitemizde toplam 62 çocuk hastaya karaciğer nakili yapılmıştır. Ortalama yaş 7,3 yıl saptandı (6,5 ay-17 yaş). Karaciğer nakil endikasyonlarının en sık 4 nedenini sırasıyla Wilson hastalığı %16,3 (10 hasta), bilier atrezi %14,5 (9 hasta), progressif familyal intrahepatik kolestaz %12,9 (8 hasta), kriptojenik siroz %11,3 (7 hasta), oluşturuyordu. Nakil sonrası mortalitemiz %19,6 oranında idi (toplam 62 hastanın 12'de). Akut rejeksiyon %34 oranında, kronik rejeksiyon ise %4,9 oranında gözlenmiştir. Tromboz %9,6 oranında gözlenmiş olup % 4,8 oranında hepatik arterde ve %4,8 oranında portal vende gözlendi. Bilier sızıntı %31 oranında gözlenmiş olup bilier darlık ise %11 oranında gözlenmiştir. Hastalarımızın 1 yıllık sağ kalımı %87 ve 5 yıllık sağ kalımı %84 saptanmıştır.

Sonuç: Organ nakli merkezimizin, çocukluk döneminde yaptığı karaciğer nakillerinin morbidite ve mortalite verileri literatür ile uyumludur.

Anahtar Kelimeler: Çocuk, karaciğer nakli, karaciğer yetmezliği

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Introduction

Liver transplantation is the only treatment option for children with acute or end-phase chronic liver disorders [1]. Regarding the irreversible liver diseases, the curative success rates of liver transplantations in childhood are higher than in adulthood [2, 3]. However, the limited availability of cadavers is the main obstacle to liver transplantations. In spite of this, almost all patients, including young patients, and patients on the cadaver waiting list are transplanted before they

die thanks to the development in surgical techniques. In addition, the recently introduced new immunosuppressive agents have enabled higher success rates after transplantation. The aim of our study was to report our experience of pediatric liver transplantation, including long-term follow-up results.

Materials and Methods

Patients aged 0–18 years that received liver transplantation in the organ transplantation center of our university hospital between 1997 and 2016 were included in the study. This study did not need to be approved by the ethical committee because this is a retrospective study conducted by the analysis of routine laboratory data; however, the research was performed according to the World Medical Association Declaration of Helsinki. This study does not include an informed consent because this study was performed by the analysis of routine laboratory data. The age, sex, indications for liver transplantation, complications after transplantation, and long-term follow-up findings were retrospectively evaluated. The obtained results were analyzed with statistical methods.

Statistical analysis

The statistical analysis was performed with Statistical Package for the Social Sciences version 15.0 (SPSS Inc.; Chicago, IL, USA). Descriptive statistics of the data mean±standard deviation for continuous variables; it is given numbers and percentages for categorical variables.

Results

In our organ transplantation center, 62 pediatric liver transplantations were performed since 1997. The etiological characteristics of our liver transplantations are listed in Table 1. The mean age of our patients was 7.3 years (6.5 months–17 years). The body weights were between 6.7 kg and 52 kg (mean=16 kg). The mean hospitalization time of our patients was 13 days and the mean stay in the intensive care unit was 3 days. The Child-Pugh score was C in 12 of our patients, B in 40 patients, and A in 10 patients. The mean PELD score was 5. The cardiac examination of our patients in the pre-transplantation period was normal and none of our patients developed hepatopulmonary or hepatorenal syndromes. The four most common indications for liver transplantation were: Wilson's disease (n=10; 16.3%), biliary atresia (n=9; 14.5%), progressive familial intrahepatic cholestasis (n=8; 12.9%), and cryptogenic cirrhosis (n=7; 11.3%). The mortality rate after transplantation was 19.6% (12 of the total 62 patients). The observed acute and chronic rejection rates were 34% and 4.9%, respectively. Thrombosis (9.6%) was observed in the hepatic artery (4.8%) and portal vein (4.8%). Bile leakage and biliary stricture rates were 31% and 11%, respectively. 1-year and 5-year survival rates of our patients were 87% and 84%, respectively. 59% (n=36) of the liver transplantations were whole liver, 5% (n=3) were split liver, 32% (n=21) were living donor transplantations and 3% (n=2) were combined liver-kidney transplantations [4].

Table 1. The etiology of liver transplantation

Diagnosis	n	%
Wilson disease	10	16.3
Biliary atresia	9	14.5
Progressive familial intrahepatic cholestasis	8	12.9
Cryptogenic cirrhosis	7	11.3
Acute liver failure	4	6.5
Glycogen storage disease	4	6.5
Autoimmune hepatitis	3	4.9
Primary hyperoxaluria type 1	4	6.5
Familial hypercholesterolemia	2	3.3
Congenital hepatic fibrosis	3	4.9
Tyrosinemia	2	3.3
Maple syrup urine disease	2	3.3
Crigler Najjar type 1	2	3.3
Alagille syndrome	1	1.2
Neonatal hepatitis	1	1.2
Total	62	100

Survival

50 of our 62 patients are still alive and followed up regularly. The 1-year and 5-year survival rates of our patients were 87% and 84%, respectively, and 12 patients had a survival rate over 10 years. 12 patients were exitus. Seven of them had received a living-donor transplant and five had received a cadaveric transplant. Although the majority of our patients had received cadaveric transplants, the majority of the exitus patients had received living-donor transplants. Two patients died because of hepatic artery thrombosis (HAT), one patient died of portal vein thrombosis (PVT), and one patient died of both HAT and PVT. 3 patients developed HAT and PVT. Two of them received a living-donor transplant and one received a cadaveric transplant. Four patients died in the early phase of the transplantation. Three of them died because of multiple organ failure, sepsis, and graft failure. A patient, who developed graft failure, died even though he had received a living-donor transplantation. One patient, who received liver transplantation due to acute liver failure, developed secondary to the aplastic anemia and died in the early phase of the transplantation as a result of humoral rejection. Another patient died due to post-transplant lymphoproliferative disease (PTLD) caused by the Epstein-Barr virus (EBV). One patient died because of the intracranial bleeding secondary to the acute rejection, and another patient died due to multiple organ failure caused by the chronic rejection. The last patient died as a result of acute kidney failure developed secondary to the polycystic kidney disease. The age interval of the exitus patients were between 9 months and 12 years, and their body weights were between 8 kg and 32 kg. The Child-Pugh score was C in 10 of the exitus patients and B in the remaining two patients. The mean PELD score was 15. Cardiac evolution of all patients was normal in the pre-transplantation period and none of them developed hepatopulmonary or hepatorenal syndrome. The mean stay in the intensive care unit and the mean hospitalization time of the exitus patients were 14 and 32 days, respectively. This data showed that the pre-transplantation scores of the exitus patients were worse than the whole patient group. Distribution of the patients who died are shown in Table 2.

Infection

After the transplantation, EBV infection emerged in 14 patients [their mean age was 16 months (6–48 months)]. The dose of the immunosuppressive treatment was reduced in these patients and oral valganciclovir treatment was administrated as an antiviral therapy. After this treatment, 9 patients became EBV-negative and

Table 2. Distribution of the patients who died

Diagnosis	n	%
Hepatic artery thrombosis	3	25
Portal vein thrombosis	1	8.3
Post-transplant lymphoproliferative disease results	1	8.3
Sepsis	4	33
Acute rejektion	1	8.3
Chronic rejektion	1	8.3
Acute renal failure	1	8.3
Total	12	100

Table 3. The observed complications after liver transplantation

Complication	n	%
Acute rejektion	21	34
Chronic rejektion	3	4.9
Hepatic artery thrombosis	3	4.8
Portal vein thrombosis	3	4.8
Post-transplant lymphoproliferative disease	1	1.1
Biliary leaks	19	31
Biliary strictures	7	11
EBV infection (permanent)	4	6.5
CMV infection (permanent)	0	0

5 patients (8%) became chronic EBV patients [5, 6]. Only one of these patients developed PTLD. The dose of the immunosuppressive treatment was reduced and rituximab was administered concomitantly with antiviral treatment in this patient [7]. However, the patient did not respond to the therapy and died. The remaining 4 patients still had chronic EBV infection and their EBV-DNA scores were lower than 2000 copies/mL. These patients, who were in good general medical condition, continue to receive reduced-dose immunosuppressive therapy and oral valganciclovir prophylaxis. As they did not show symptoms of active disease, rituximab treatment was not initiated. We encountered cytomegalovirus (CMV) infection in 6 of our patients after transplantation. Their mean age was 19 months (6–48 months). All of the cases recovered completely after the initial intravenous (10 mg/kg/day) ganciclovir and then p.o. valganciclovir treatment was given.

Vascular Complications

After transplantation, in 6 patients [HAT, n=3 (4.8%); PVT, n=3 (4.8%)] acute vascular obstruction was encountered and one of them died due to the both HAT and PVT. 2 patients with vascular obstruction developed HAT and they applied for re-transplantation; but they died as no matching living or cadaveric donor was found. In one patient who developed PVT, surgical revision was carried out; but he died as no improvement was elicited. The remaining patients, who developed PVT, recovered after surgical revision and anticoagulant treatment. Regarding acute rejection, 21 attacks occurred in 14 of our patients (34%). 18 attacks recovered with the intermittent pulse dose of intravenous methylprednisolone. In 3 attacks, the patients responded to the combined treatment with antithymocyte globulin (ATG) and intermittent pulse methylprednisolone [8]. One of the three patients who had chronic rejection died due to the multiple organ failure. The other two patients were treated with pulse doses of IV methylprednisolone, tacrolimus, mycophenolate mofetil, and ursodeoxycholic acid. As they did not recover, sirolimus treatment was initiated and they are still on the waiting list for a second liver transplantation [9].

Biliary Complications

We encountered biliary complications in 26 of the 62 patients (42%) and we performed surgical revision due to anastomosis leakage in 19 patients (31%). In the remaining 7 patients (11%), biliary stricture emerged. In one patient, a stent was inserted with endoscopy; in four patients, a stent was inserted with percutaneous drainage; and in two patients, open drainage was carried out. The observed complications after liver transplantation are shown in Table 3.

Discussion

The most common indications for liver transplantation in our patients were Wilson's disease (16.3%), biliary atresia (14.5%), progressive familial intrahepatic cholestasis (PFIC) (12.9%), and cryptogenic cirrhosis (11.3%). As the most frequently reported indication in the literature was Wilson's disease, and it is followed by biliary atresia, our results were consistent with the literature [10, 11]. According to the statistics of the Organ Procurement and Transplantation Network in the USA, 1-year and 5-year mean survival rates in pediatric liver transplants are between 91%–91.4% and 84%–86.5%, respectively [12, 13]. Our results (87% and 84%) are in accordance with the results reported in the literature.

After transplantation, persistent EBV and CMV infection rates in our patients were 8% and 0%, respectively. In the study of Oh et al. (10), the EBV and CMV infection rates in the patients investigated after 2003 were 41.2% and 9.2%, respectively. However, Oh et al. [14] did not report any mortality due to PTLD. In our study, one patient died because of PTLD (1.6%).

There is a high risk of thrombosis in the hepatic artery anastomosis (5%–18%) and it often causes graft necrosis in the early phases. HAT emerged 3 to 4 times more frequently in children than in adults. It was encountered even in whole liver transplantations of small infants and usually emerged within the first 30 days [15]. The reported average HAT rates were between 4% and 6% in pediatric liver transplantations, and it was 4.8% in our study [16]. The reported average PVT rates were 5%–10% in the literature, and the same rate in our patients was 6.4% [17].

In the first weeks of the liver transplantations, acute rejection rates were between 20% and 50% in the literature, and the same rate was 34% in our study [18]. The chronic rejection rate in the study of Oh et al. [14], which was conducted with 200 patients, was 3.4%. It was 4.9% in our study.

Biliary complication rates in the pediatric liver transplantations were between 10% and 30%, although it might be affected by the type of the allograft. In our study, bile leakage and biliary stricture rates were 31% and 11%, respectively (total rate of the biliary complications was 42%) [19, 20].

In conclusion, the morbidity and mortality results in our organ transplantation center regarding liver transplantations in childhood

were consistent with the results in the literature. We believe that, as a consequence of the developments in surgical techniques, introduction of new and effective immunosuppressive agents, and increased expertise of the healthcare team, less complications will emerge in pediatric liver transplantations; and thus, more liver transplantations will be carried out in the future.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: This study doesn't include an informed consent, because this study is performed by the analysis of routine laboratory data.

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