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SINGLE CENTER EXPERIENCE OF LIVER RE-TRANSPLANTATION: INDICATIONS-TIMING AND COMPLICATIONS

KARACİĞER RE-TRANSPLANTASYONU TEK MERKEZ DENEYİMİ: ENDİKASYONLAR-ZAMANLAMA VE KOMPLİKASYONLAR

Cihan KARATAŞ[1], Altan ALİM[2], Akın AKBULUT[1], Barış DEMİR[1], Bahadır Hakan OĞUZ[2], Turan KANMAZ[1]

[1]Koc University Hospital, Department of Liver Transplantation, İstanbul, Türkiye
[2]Koc University Hospital, Department of Anesthesiology, İstanbul, Türkiye

ORCID IDs of the authors: C.K. 0000-0003-1385-741X; A.A. 0000-0002-2739-7445; A.A. 0000-0003-2999-7484; B.D. 0000-0002-2053-0469; B.H.O. 0000-0001-6464-0582; T.K. 0000-0003-1886-7721

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ABSTRACT

Objective: Function loss, for whatever reason, of the graft used for liver transplantation requires re-transplantation. This study is an evaluation of all re-transplantations performed at our center.

Material and Method: All liver re-transplantation patients whose surgeries had been performed at our clinic, whether at an early or late stage, were included in the study. Demographic information, details related to the surgery, and complications were evaluated retrospectively.

Result: From 2018 to 2023, 236 liver transplantations were performed on 228 recipients in our institution. Of these patients, a total of 18 underwent re-transplantation, 10 of whom were from external centers and 8 of whom had had their first liver transplantation performed at our center. Of these patients, 12 were male and 6 were female, with a mean age of 6.7 years (±4.8) for pediatric patients and 49 years (±14.32) for adult patients. The mean weight for pediatric patients was 19.76 kg (±8.86), and for adult patients it was 70.48 kg (±11.83). The mean body mass index for pediatric patients was 17.41 kg/m² (±2.84), and for adult patients it was 22.33 kg/m² (±2.65). Six of these patients underwent early re-transplantation (7.6±5.4 days) and 12 underwent late re-transplantation (7.6±5.3 years). In terms of re-transplantation etiology, primary non-function was prominent for the early period, while secondary biliary cirrhosis, disease recurrence, and chronic rejection were detected for the late period. Seven recipients (39%) died during the perioperative period, and 1-year survival was calculated as 61% in this patient group.

Conclusion: Re-transplantation has high mortality and morbidity rates. Although early re-transplantation seems to overcome

ÖZET

Amaç: Karaciğer transplantasyonu için kullanılan greftin çeşitli nedenlerle fonksiyon kaybı re-transplantasyonu gerektirmektedir. Bu çalışmada merkezimizde gerçekleştirilen tüm karaciğer re-transplantasyon olguları değerlendirilmiştir.

Gereç ve Yöntem: Kliniğimizde erken ve geç dönem olmak üzere karaciğer re-transplantasyonu yapılan tüm hastalar çalışmaya dahil edildi. Demografik bilgiler, ameliyatla ilgili detaylar ve komplikasyonlar retrospektif olarak değerlendirilmiştir.

Bulgular: 2018'den 2023'e kadar kurumumuzda 228 alıcıya 236 karaciğer nakli gerçekleştirildi. Bu hastalardan 10'u dış merkezlerden olmak üzere toplam 18 hastaya re-transplantasyon yapılmıştır. Bu hastaların 12'si erkek, 6'sı kadın olup, yaş ortalaması pediatrik hastalarda 6,7 (±4,8), erişkin hastalarda ise 49 (±14,32) idi; çocuk hastaların ortalama ağırlığı 19,76 kg (±8,86), yetişkin hastaların ortalama ağırlığı 70,48 kg (±11,83); çocuk hastaların ortalama vücut kitle indeksi 17,41 kg/m² (±2,84), yetişkin hastaların ise 22,33 kg/m² (±2,65) olduğu belirlendi. Bu hastaların altısına erken retransplantasyon (7,6±5,4 gün), 12'sine geç retransplantasyon (7,6±5,3 yıl) uygulandı. Re-transplantasyon etiyolojisi açısından erken dönemde primer non-fonksiyon ön plana çıkarken, geç dönemde sekonder biliyer siroz, hastalık nüksü ve kronik rejeksiyon saptandı. Perioperatif dönemde yedi alıcı (%39) öldü ve bu hasta grubunda 1 yıllık sağkalım %61 olarak hesaplandı.

Sonuç: Re-transplantasyon yüksek mortalite ve morbidite oranlarına sahiptir. Erken re-transplantasyon, özellikle primer non-fonksiyon vakalarında yüksek ölüm oranlarının üstesinden

Corresponding author/İletişim kurulacak yazar: Cihan KARATAŞ – ckaratas@kuh.ku.edu.tr

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high mortality rates, especially in primary non-function cases, organ shortage and the need for living donors are significant problems.

Keywords: Liver transplantation, chronic graft dysfunction, liver re-transplantation

geliyor gibi görünse de, kadavra organ eksikliği ve canlı donör ihtiyacı önemli sorunlardır.

Anahtar Kelimeler: Karaciğer nakli, kronik greft disfonksiyonu, karaciğer re-transplantasyonu

INTRODUCTION

Liver transplantation (LT) surgery, which started in the 1960s, has shown an increase in graft and patient survival and a decrease in complication and mortality rates due to the improvement of surgical techniques and technological developments in gastroenterology, endoscopic procedures, immunology, microbiology, pharmacology and especially interventional radiology (1, 2).

Graft and patient survival are the most important goals in LT. The most important factors affecting graft and patient survival are surgical technique, primary non-function (PNF), recurrence of primer disease, rejection (acute or chronic), and bile duct anastomosis complications (3-5). When the graft is irreversibly severely affected and becomes dysfunctional, re-transplantation (Re-Tx) becomes a life-saving option if the clinical condition of the patient is appropriate.

For both surgical and medical reasons, liver Re-Tx has a lower success rate than the initial transplant, and a 1-year survival rate has been reported to be around 77% for adult patients and 89% for pediatric patients (6-8). The worldwide average Re-Tx rate among all liver transplants varies between 7% and 23% (9).

In this study, liver Re-Tx cases performed at our clinic were retrospectively evaluated, and the results obtained are shared.

MATERIALS and METHODS

Patients who underwent Re-Tx from July 2018 to February 2023 were included in this study. The patient group was divided into two categories, "early" and "late", and their demographic data, etiology of LT (first LT and Re-Tx), graft type and characteristics, vascular and biliary anastomosis types, amount of replaced blood during surgery, length of hospital stay, and complications/mortality were noted. Re-Tx performed within the first month after LT is defined as early Re-Tx, and Re-Tx performed one month later is defined as late Re-Tx (10).

Recipient and donor preparation (if a living donor was used), postoperative immunosuppression treatment, and long-term patient follow-up were performed according to clinical protocols (11).

This study was approved by Koç University Ethic Committee (Date: 21.06.2023, No: 2023.223.IRB1.073).

Statistical analysis

IBM SPSS 21 statistical package program was used for data evaluation (IBM SPSS Corp., Armonk, NY, USA). As the data did not follow a normal distribution, median (minimum-maximum values) and mean±standard deviation were provided. Kaplan-Meier was used for survival statistics.

RESULTS

Between July 2018 and February 2023, 236 LTs were performed at our center on 228 patients (103 children, 125 adults). Seventeen patients underwent a first Re-Tx surgery, and one patient underwent a second Re-Tx. Of these Re-Tx patients, six were female and 12 were male, and there were 12 pediatric and six adult patients.

The mean age for the pediatric patients who underwent a Re-Tx was 6.7 years (±4.8), and for adult patients it was 49.08 years (±14.32). The mean weight for pediatric patients who underwent a Re-Tx was 19.76 kg (±8.86), and for adult patients it was 70.48 kg (±11.83). The mean body mass index for pediatric patients was 17.41 kg/m² (±2.84), and for adult patients it was 22.33 kg/m² (±2.65). Re-Tx was performed urgently on 6 patients, and electively on 12 patients. All of the six patients who underwent an early urgent Re-Tx and two of the 12 patients who underwent a late Re-Tx had had their first LT at our clinic.

The patients' demographic information, initial transplant indications, and re-transplantation reasons are detailed in Table 1. Vascular thrombosis and PNF were the prominent etiologies in patients who underwent early urgent Re-Tx, while chronic rejection and secondary biliary cirrhosis were more common in patients who underwent late surgery.

The mean time between the initial transplant and Re-Tx was 8.3 days (±5.1) for early Re-Tx and 7.7 years (±5.4) for the late group. Preoperatively, all the cases of the early group and one patient of the late group were followed in the intensive care unit. The liver grafts used in Re-Tx included two whole livers from deceased donors (11%), three split left lateral segments from deceased donors (16%), one split right lobe from a deceased donor (5.5%), six living donor left lateral segments (33%), five living donor right lobes (27%), and 1 living donor left lobe (5.5%). The graft weights were a mean of 607 g (±436) with a body weight-to-graft weight ratio of 1.6% (±0.6).

Cadaveric allograft vein replacement was performed in two of the portal vein anastomoses. Hepatic artery anastomosis was performed under a microscope (Leica M530 OHX,

Table 1: The patients' demographic information, initial transplant indications, and Re-Tx reasons. The first six patients are early Re-Tx patients, the others are late Re-Tx patients

	Age (Year)	Gender (M/F)	Weight (kg)	BMI (kg/m²)	Etiology	Reason of Re-Tx
1	48	1	56	18.5	PSC	PNF
2	1.5	1	13.1	20.5	Wolcott - Rallison syndrome	PNF
3	0.5	2	10.8	19.7	Argininosuccinic acidemia	PVT
4	8.5	2	17.6	16.6	Cryptogenic cirrhosis	HAT
5	2.5	1	9.9	13.7	Alagille syndrome	PNF
6	6	2	20	15.7	Biliary atresia/HPS	PV injury/acute liver failure
1	48	1	89.5	26.2	PSC	Secondary biliary cirrhosis
2	6	2	22.5	18.9	Primary Hyperoxaluria	Sekonder Budd Chiari
3	11	1	30	17.8	Biliary atresia	Secondary biliary cirrhosis
4	6.5	2	17.4	15.8	Criggler Najar syndrome	Secondary biliary cirrhosis
5	4	1	12.9	14	Biliary atresia	Chronic rejection
6	66	1	74	24.2	Alcoholic cirrhosis	HCV
7	23.5	1	64.7	20.9	FAH	HBV
8	51	1	75.7	22.1	Wilson/Chronic rejection	Chronic rejection
9	58	1	63	22.1	HBV	Chronic rejection
10	15	2	33	14.7	Primary Hyperoxaluria	Chronic rejection
11	4	1	14	23	Primary Hyperoxaluria	Chronic rejection
12	15	1	36	18.6	PFIC	Chronic rejection

FAH: Fulminant Autoimmune Hepatitis, HAT: Hepatic Artery Thrombosis, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, HPS: Hepatopulmonary Syndrome, PFIC: Progressive familial intrahepatic cholestasis, PNF: Primary non-function, PSC: Primary Sclerosing Cholangitis, PV: Portal Vein, PVT: Portal Vein Thrombosis, M/F: Male/Female

Table 2: Detailed information about patients who underwent early and late Re-Tx is summarized.

	Early Re-tx	Late Re-tx
Age (years)	11.2 (±18.2)	25.7 (±23.3)
Weight (kg)	21.2 (±17.4)	44.4 (±27.2)
BMI (kg/m²)	19.0 (±3.6)	19.9 (±3.9)
Op. Time (minutes)	371 (±122)	516 (±116)
Blood tx (ml)	1379 (±1153)	1445 (±1139)
Re-tx type	Deceased full-sized (1) Deceased split LL (2) Live donor LL (3)	Deceased full-sized (1) Deceased split right (1) Deceased split LL (1) Live donor right (5) Live donor left (1) Live donor LL (3)
1-year survival	33.30%	75.00%
Reason of mortality	Intraabdominal sepsis (2) Postoperative brain death (1) Vascular collapse (1)	Intraabdominal sepsis (3)

BMI: Body mass index, LL: Left lateral, Op: Operation, Re-tx: Re-transplantation.

Singapore) using 7-8/0 polypropylene as continuous-interrupted techniques with 5-10x magnification. Double artery anastomosis was needed in two patients. The biliary reconstruction was completed with duct-to-duct in two adult cases and Roux-en-Y hepaticojejunostomy in other cases.

The mean operation time for all patients was 467 (±134) minutes, and the mean blood transfusion requirement was 1422 (±1102) ml/m². Detailed information on the patients is summarized in Table 2.

The one-year survival rate was 61.1%, with rates of 33.3% for early and 75% for late Re-Tx. All mortalities were seen in the early perioperative period. The reasons for the mortalities were intraabdominal sepsis in five cases, postoperative brain death in one case, and hemodynamic instability and vascular collapse in one.

As for surgical complications, spontaneous intestinal perforation was seen in three patients, diaphragmatic hernia in one, portal vein stenosis in two, and hepatic artery stenosis in one during the early postoperative period. During the late period, bile duct anastomosis stenosis was seen in two patients, PTLD in one, and osteomyelitis in another.

The average length of hospital stay for surviving patients was 31.3 days (±24.7), and the mean follow-up period was 2.5 years (±1.3).

DISCUSSION

Liver Re-Tx, which was first applied in 1981, has developed over the years and success rates have increased. As a result, the need for Re-Tx has decreased and survival rates of Re-Tx have increased. 5-year survival rates have been reported to vary between 60% and 80% (6-8). Re-Tx rate after the first LT varies between 7% and 23% according to different sources (9, 12, 13).

Re-Tx performed within the first month after LT is defined as early Re-Tx, while Re-Tx performed after one month is called late Re-Tx (10). The most common causes of early Re-Tx are primary non-function and vascular complications, whereas disease recurrence and biliary complications are the most common causes of late Re-Tx (14, 15).

Both technical and medical problems increase morbidity and mortality in Re-Tx and have a higher complication rate compared to initial LT (6). The combination of adhesions and fibrosis caused by previous operations, the length and quality of the remaining inferior vena cava, hepatic artery, portal vein and bile ducts, and portal hypertension caused by previous operations may particularly increase the rates of bleeding and complications (16, 17). However, elective surgery in late Re-Tx cases, especially those performed with a living donor, leads to more satisfactory haemodynamic and metabolic control (9).

Although early Re-Tx does not have many of the same surgical challenges, metabolic and haemodynamic problems in emergency LT may lead to complications. Therefore, although early Re-Tx has a shorter operative time, for patient-related reasons, mortality is higher than in patients who undergo early Re-Tx (9, 18, 19).

In some cases, depending on the severity of graft liver necrosis, the metabolic and haemodynamic status of the recipient may deteriorate. This is caused by cytokines and vasoactive agents released from the necrotic liver into the systemic circulation. This clinical picture, also known as "Toxic Liver Syndrome", may lead to multiorgan dysfunction (20). In such patients, graft hepatectomy may be necessary to remove the toxic liver from the body. This allows time for the patient to undergo Re-Tx. In the an-hepatic period, the patient is supported with plasma exchange and haemodiafiltration/haemodialysis and monitored in the intensive care unit (21). One of our patients required graft hepatectomy. The "an-hepatic period" lasted approximately 18 hours and the patient benefited from liver Re-Tx.

In continents where organ donation is low, such as Central Asia and the Far East, deceased donor organ restrictions affect the survival of patients requiring urgent Re-Tx. According to the data from the Turkish Ministry of Health, the organ donation/brain death rate in 2022 is around 16.8% (22). Due to insufficient organ donations, living donor LT becomes mandatory, especially in cases requiring urgent Re-Tx. The willingness of family members to donate organs for a second living donation, finding a suitable donor and preparing the donor may cause significant time loss. In cases of acute liver failure with severe haemodynamic and metabolic problems, lost hours increase patient mortality.

In our clinical experience, when emergency Re-Tx is planned with a living donor, the time required to complete the investigations is 4 hours, but the actual time loss depends on the decision of the family and the voluntary donation of the living organ. In two cases in which emergency surgery was required from living donors, one case resulted in postoperative brain death due to delayed preparations, and the other case resulted in early postoperative death due to haemodynamic instability and metabolic problems.

One of the most important disadvantages of this study is its retrospective and single-center design. Also, the sample size of the study is too small to allow a statistical comparison. Nevertheless, the results of the study provide valuable information for liver Re-Tx.

CONCLUSION

Re-Tx has a higher mortality and complication rate compared to initial LT especially in emergency Re-Tx cases.

The scarcity of organ donations and the need for living donors cause loss of time and seem to be the most important mortality factors. In late Re-Tx cases, despite surgical technical difficulties, metabolic and haemodynamic stabilization of the patient and planning the operation under elective conditions result in positive outcomes. Re-Tx with a living donor is advantageous due to appropriate timing and patient preparation.

Ethics Committee Approval: This study was approved by Koç University Ethic Committee (Date: 21.06.2023, No: 2023.223.IRB1.073).

Informed Consent: This is a retrospective archive study that does not include live animals or humans. Therefor informed consent was not sought.

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