

Liver retransplantation: 6 years of experience of the Hospital Pablo Tobón Uribe

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Abstract

Objectives: Liver retransplantation is the only therapeutic option for liver graft failure which occurs in 5% to 23 % of all transplants. Graft failure is associated with poorer survival rates and increased complications and costs. The objectives of this study were to assess the incidence of liver retransplantation and describe complications and survival of liver retransplantation patients at a center in Colombia.

Materials and Methods: This was a retrospective descriptive study of patients retransplanted at the Hospital Pablo Tobón Uribe between 2004 and 2010.

Results: Three hundred five adults and children underwent orthotopic liver transplants between 2004 and 2010. Liver retransplantation was performed on 21 adult patients (7.7 %). The main indication was thrombosis of the hepatic artery. Patient survival at 1 year was 81 %, and at 5 years it was 76 %. Liver graft survival was at one year was 76 % and at five years was 72%. Vascular complications were found in 4 patients (19%), and biliary complications were found in 4 patients (19%). Infections were documented in 11 patients (52 %). The main cause of death was primary liver graft dysfunction.

Conclusion: Liver retransplantation is a complex procedure requiring great technical skill and appropriate patient selection. Medium term results in the Hospital Pablo Tobón Uribe in Medellín are similar to those reported in the literature.

Keywords

Liver transplantation, retransplantation, graft failure.

INTRODUCTION

Liver transplantation is currently considered the treatment of choice for chronic liver disease and acute liver failure (1). Liver retransplantation is the only definitive treatment option in chronic graft dysfunction no matter what the cause. It is considered that 5% to 23% of all transplants performed are retransplants (2). Data from the European Liver Transplant Registry (ELTR) till December 2010 show that 10.3% of 98,098 transplants were liver retransplants (3). Overall, retransplantation is associated with poorer survival, with major complications and higher costs

than first transplants (4, 5). Questions exist about this intervention on the basis of its results when the limited availability of cadaveric organs and the possibility that candidates on the waiting list for first time liver transplantation will die are taken into account. Currently, numerous forecasts models such as the Rosen score and MELD facilitate identification of patients with poor prognoses which helps avoid futile interventions (6, 7, 8). In Colombia there has been no information regarding results for these patients, which is why the liver transplantation group experience of the Pablo Tobón Uribe Hospital in Medellín, Colombia is being reported.

PATIENTS AND METHODS

All demographic data as well as morbidity and mortality rates were obtained by retrospective reviews of the liver transplantation medical records and database. Data was with collected for patients who underwent liver retransplantation between 2004 and 2010. Patients were selected using the conventional assessment protocol established for liver transplantation plus MELD and modified Rosen scores. The surgical technique in our center was similar to that applied in the first transplant patients. We use the piggy-back technique, portal vein and hepatic artery end to end anastomosis, even in patients with hepatic artery thrombosis or ischemic cholangiopathy. When deemed necessary by the surgeon, an arterial graft was performed with a donor iliac artery to the infrarenal abdominal aorta. The conventional biliary anastomosis for retransplantation was hepatic-jejunostomy. All patients were transferred postoperatively to the intensive care unit (ICU) where the early extubation protocol was implemented. Most patients with liver retransplantation received immunosuppression similar to the first liver transplant patients (cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil and steroids). The exceptions were patients with chronic liver graft rejection or autoimmune disease recurrences. In these cases Tacrolimus, Mycophenolate mofetil and steroids were used for immunosuppression. In patients who tolerated the graft, steroids were suspended 3 to 6 months after the procedure. In cases of moderate acute or severe rejection confirmed by biopsy, patients were treated with methylprednisolone boluses.

Statistical analysis was based on socio-demographic and clinical variables of patients in the study. These included pre transplant conditions, retransplantation indications, intraoperative variables, postoperative variables such as complications, ICU days, length of hospital stay, graft survival and patient survival. First, the type of distribution of each variable was checked and bivariate analysis was performed using the χ^2 test for categorical variables and the nonparametric Mann-Whitney U test to compare ranges between independent groups. A survival analysis using the Kaplan Meier curve for the outcomes of graft losses and patient deaths at one and five years was performed.

This study was approved by the hospital's medical ethics committee.

RESULTS

From February 2004 to December 2010, 305 orthotopic liver transplants were performed in children and adults at the Pablo Tobón Uribe Hospital in Medellín. All transplanted organs came from cadaveric donors. Liver retrans-

plantation was performed in 21 adult patients (7.7%). All transplants were performed with the piggy-back technique and end to end anastomosis of the portal vein. No patient required veno-venous bypass. The hepatic artery anastomosis was an arterial graft in 66% of patients and the biliary anastomosis was liver-jejunostomy in 77% of patients.

The average age of recipients was 49 years (26-70 years), and 76% were male. The average MELD was 16 and the average modified Rosen score was 14. Sixty-six percent of the patients were retransplanted within 30 days of the first transplantation. The indications for liver retransplantation can be seen with other perioperative variables in Table 1. The most important indication was hepatic artery thrombosis. In all of these cases retransplantation was performed within 7 days of the first transplantation. Recurrence of hepatitis C was the indication in one patient.

Table 1. General liver retransplantation patients characteristics in Pablo Tobón Uribe Hospital, Medellín from 2004-2010.

Feature	Total No: 21
Male	16 (76%)
Female	5 (24%)
Age	49 years (28-70 years)
MELD	16 (7 to 34)
Rosen	14 (8 to 20)
Interval between first transplantation and retransplantation	7 days or under: 4 patients 7 to 30 days: 3patients 30 days or more: 14 patients
Indication	
Hepatic artery thrombosis	7 (33%)
Ischemic cholangiopathy	6 (28%)
Chronic rejection	5 (24%)
Disease Recurrence	2 (10%)
Primary dysfunction	1 (5%)
Donor age	33 (18-60)
Time on waiting list	16 days (1-60)
Cold ischemia time	322 minutes
Warm ischemia time	31 minutes
Hospital Stay	
Intensive care unit	7 days
Hospitalization	17 days

The patient survival rate was 81% at one year and 76% at five years (Figure 1). The liver graft survival rate at one year was 76% and 72% at five years. The main cause of death was primary liver graft dysfunction which occurred in three patients, all within the first 7 days following transplantation. One patient died of septic shock four months after transplantation, and another patient died as the result of chronic rejection refractory to treatment with severe hepatic graft dysfunction two years after transplantation.

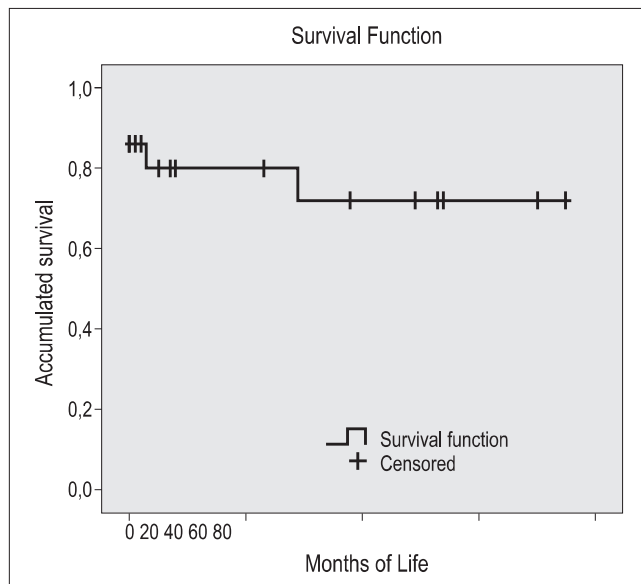


Figure 1. Liver retransplantation patients survival in the Pablo Tobon Uribe Hospital from 2004-2010.

Significant postoperative bleeding in 14% of patients required a second surgical intervention. Other perioperative, vascular and biliary complications are described in Table 2. Four patients had primary liver graft dysfunction, all were carriers of arterial grafts which had no documented vascular events. One patient improved spontaneously. Hepatic artery thrombosis was documented in a patient who was an arterial graft carrier with a complex reconstruction which joined two iliac vessels grafts. This patient required an early liver transplant.

Nineteen percent of patients presented biliary complications. Three patients with anastomotic stenosis of liver-jejunosotomy required treatment with internal-external biliary bypasses. None of the five patients with choledochocholedochostomy type biliary anastomosis had biliary complication during follow-up, although 2 of these patients died early due to primary graft dysfunction.

Infections were documented in 11 patients (52%). Seventy percent of these were bacterial origin, and of these the origin was in the abdominal cavity in 75% of cases. A patient who died of abdominal sepsis presented concomitant disseminated tuberculosis.

Acute rejection developed in 6 patients (28%), although 80% of these developed early and responded well to treatment. Chronic rejection was documented in one patient who was refractory to treatment. Chronic renal failure occurred in five patients (24%) and disease recurred in one patient (5%).

Table 2. Complications following liver retransplantation post at the Pablo Tobón Uribe Hospital from 2004-2010

Feature	Total No: 21 patients
Perioperative complications	
Bleeding	3 patients (14%)
Reperfusion syndrome	2 patients (10%)
Primary graft dysfunction	4 patients (19%)
Vascular Complications	4 pacientes (19%)
Hepatic artery	
Thrombosis	1
Stenosis	1
Portal vein	
Thrombosis	1
Hepatic vein and Vena cava	
Stenosis	1
Biliary complications	4 patients (19%)
Anastomotic stenosis	3
Non Anastomotic stenosis	1
Infectious complications	11 patients (52%)
Bacterial Infections	8
Cytomegalovirus	1
Herpes infection	1
Tuberculosis	1

DISCUSSION

Liver transplantation has become an established therapy for acute liver failure and for chronic liver failure (1). With the increasing number of liver transplants there is also increased demand for retransplantation which has led to debate in the scientific community because survival outcomes are worse for retransplantation and because of the limited availability of organs and the potential for deaths of first liver transplant patients on the waiting list (4, 5).

The incidence of liver retransplantation in this study was 7.7%. Retransplantation rates reported in other studies range from 5% to 23%. The average in European and American records is 10%, so our incidence is similar to that described elsewhere (3, 9).

In this study, the 5-year patient survival rate was 76% and the 5-year liver graft survival rate was 72%. Phitzmann recently published a 5-year patient survival rate of 67% (10), Marudanayagam et al. published a 5-year patient survival rate of 57% and Hong et al. published a 5-year patient survival rate of 48% (11, 12). In fact, our study's 5-year survival rate for liver retransplantation patients is comparable with the results of first liver transplantation patients whose 5-year survival rate was 72% (results in press). Our results are similar to the 73.8% 5-year patient survival rate reported by Thuluvath et al. in a long-term study of American centers (OPTN/SRTR data) (9). Although

our patient survival results are similar to, and even a bit better than, those described for retransplantation in other centers elsewhere in the world, this information should be analyzed carefully. When the data from the original studies is reviewed, the ages of patients and transplantation indications are similar, but patients in other studies have been more seriously impaired with average MELD scores between 22 and 30 (whereas the MELD average was 16 in our series) and there have been long waiting times and older donors (10, 11, 12). We believe that our rigorous selection of patients for liver retransplantation in which patients that have the greatest probabilities of success are chosen is the largest factor explaining the results described in this study.

Deciding whether or not a patient should receive a retransplant is a very difficult decision for any liver transplant group anywhere in the world. The decision to assign patients to the waiting list and the decision to perform a transplant are based on the two fundamental principles of fairness and justice but also must take into account other principles such as autonomy, non-maleficence, utility and dignity (13).

Clinicians should be aware that there are other patients on the waiting list for first transplants, that economic resources are limited, and that these resources should be distributed equally among all patients, and that they should attempt to obtain the greatest net benefit for society. They must avoid futile procedures by considering the relatively clear international refusal to offer liver transplantation to any patient whose 5-year survival prognosis is less than 50% (14). Nowadays there are various prognostic models that can help with this prediction, although none of them are universally accepted. One of the most commonly used is the Rosen score which is a logarithmic measurement of variables such as patient age, total bilirubin, creatinine, and the interval time from the first transplant. It was created with information from the UNOS database and was validated and modified in 2003 (6, 7). Rosen scores classify patients as low risk of death (score less than 16), intermediate risk (score of 16 to 20.5) and high risk of death (score > 20.5). Five year survival rates for patients scoring low or intermediate risks have been greater than 50%. MELD scores of over 25 are related to survival rates of less than 60% at 1 year and less than 40% at 5 years, especially if the recipient age is 50 or older (8). In our series, the average Rosen score was 14, the average MELD score was 16, and the average patient age was 49 years.

Hepatic retransplantation results according to the time elapsed after the first transplantation have also been described. Some studies have found that the risk of death is higher after early retransplantation (first 30 days). A series of Busuttil et al. that analyzed data from more than 3,000 liver transplants showed that the highest death rate following

retransplantation occurred in the time period from 8 to 30 days after primary transplantation with lower probabilities of patient death within the first 7 days and after 30 days had passed (15). In our series, most retransplantation patients were late (after 1 month).

Causes of retransplantation can be divided into early (first 30 days) and late (after 30 days). Primary graft dysfunction and hepatic artery thrombosis are included in the first group. Ischemic cholangiopathy, chronic rejection and underlying disease recurrence are included in the later. In this series, the main retransplantation cause was hepatic artery thrombosis which occurred in 33% of patients. This is similar to that reported recently by Marudanayagam et al. (11) although there was a lower percentage of hepatitis C recurrence than described in other studies (2, 12). This last point is important because recurrence of hepatitis C is associated with a 30% lower survival rate than other retransplantation causes (16). Aggressive recurrence of hepatitis C (fibrosing cholestatic hepatitis) is often considered to be a contraindication for retransplantation especially for patients who do not respond to antiviral therapy. Fortunately, hepatitis C infection is not common in our environment and accounts for only 12% of all patients transplanted at this center.

The main cause of death in this study was primary liver graft dysfunction with multiple organ failures and rapid onset that prevented urgent retransplantation. In other series elsewhere in the world, the main cause of death is early sepsis (12). The percentage of infectious, vascular and biliary complications in our study is similar to that reported by Pfitzmann et al. although it should be noted that our patients had fewer episodes of severe bleeding and reoperation (10). We also highlight that in recent years choledochocholedochostomy biliary anastomosis has been chosen, which until now has not been associated with increased number of biliary complications.

This study has several limitations. The most important are the retrospective design which limited our ability to describe these patients' characteristics and outcomes, the small number of patients included in the study, and the medium term follow-up of these patients. The liver transplant group is relatively young, so it was not feasible to analyze these patients by time periods. A case and control study was also impossible because there was no comparable group of patients who had undergone only first liver transplants to use as a control group.

Finally, we believe that appropriate patient selection for liver retransplantation with tools like the MELD and the Rosen score and improvements in surgical technique and perioperative care are key factors for improving medium and long term outcomes in this particular patient group.

In conclusion, liver retransplantation is a complex procedure associated with a greater number of complications

and with outcomes that are not as good as those of first transplants at our center. Medium-term results are similar to those described in other centers elsewhere in the world.

REFERENCES

1. Murray KF, Carithers RL Jr, AASLD. AASLD practice guidelines: Evaluation of the patient for liver transplantation. *Hepatology* Baltim Md. 2005;41(6):1407-32.
2. Lerner S, Markmann J, Jurim O, Busuttil RW. Retransplantation. En: Busuttil RW, Klintmalm GB, Editores. *Transplantation of the liver*. 2.^a edición. Philadelphia: Saunders; 2005. p. 767-775.
3. European Liver Transplant Registry - ELTR [Internet]. [citado 2 de junio de 2014]. Recuperado a partir de: <http://www.eltr.org/spip.php?article192>
4. Doyle HR, Morelli F, McMichael J, Doria C, Aldrighetti L, Starzl TE, et al. Hepatic Retransplantation--an analysis of risk factors associated with outcome. *Transplantation*. 1996;61(10):1499-505.
5. Markmann JF, Markowitz JS, Yersiz H, Morrissey M, Farmer DG, Farmer DA, et al. Long-term survival after retransplantation of the liver. *Ann Surg*. 1997;226(4):408-418; discussion 418-20.
6. Rosen HR, Madden JP, Martin P. A model to predict survival following liver retransplantation. *Hepatology* Baltim Md. 1999;29(2):365-70.
7. Rosen HR, Prieto M, Casanovas-Taltavull T, Cuervas-Mons V, Guckelberger O, Muiesan P, et al. Validation and refinement of survival models for liver retransplantation. *Hepatology* Baltim Md. 2003;38(2):460-9.
8. Watt KDS, Lyden ER, McCashland TM. Poor survival after liver retransplantation: is hepatitis C to blame? *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc*. 2003;9(10):1019-24.
9. Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999-2008. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2010;10(4 Pt 2):1003-19.
10. Pfitzmann R, Benschmidt B, Langrehr JM, Schumacher G, Neuhaus R, Neuhaus P. Trends and experiences in liver retransplantation over 15 years. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc*. 2007;13(2):248-57.
11. Marudanayagam R, Shanmugam V, Sandhu B, Gunson BK, Mirza DF, Mayer D, et al. Liver retransplantation in adults: a single-centre, 25-year experience. *HPB*. 2010;12(3):217-24.
12. Hong JC, Kaldas FM, Kositamongkol P, Petrowsky H, Farmer DG, Markovic D, et al. Predictive index for long-term survival after retransplantation of the liver in adult recipients: analysis of a 26-year experience in a single center. *Ann Surg*. 2011;254(3):444-8; discussion 448-9.
13. Biggins SW. Futility and rationing in liver retransplantation: when and how can we say no? *J Hepatol*. 2012;56(6):1404-11.
14. Neuberger J, Gimson A, Davies M, Akyol M, O'Grady J, Burroughs A, et al. Selection of patients for liver transplantation and allocation of donated livers in the UK. *Gut*. 2008;57(2):252-7.
15. Busuttil RW, Farmer DG, Yersiz H, Hiatt JR, McDiarmid SV, Goldstein LI, et al. Analysis of long-term outcomes of 3200 liver transplantations over two decades: a single-center experience. *Ann Surg*. 2005;241(6):905-916; discussion 916-18.
16. Pelletier SJ, Schaubel DE, Punch JD, Wolfe RA, Port FK, Merion RM. Hepatitis C is a risk factor for death after liver retransplantation. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc*. 2005;11(4):434-40.